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Attorneys for Plaintiff
MONSTER ENERGY COMPANY, a Delaware corporation

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

MONSTER ENERGY COMPANY, a Delaware corporation,

Plaintiff,

vs.

VITAL PHARMACEUTICALS, INC. c/b/a VPX Sports, a Florida corporation, and JOHN H. OWOC a.k.a. JACK OWOC, an individual ,

Defendants.

Case No. 5:18-cv-1882-JGB-SHK

EXHIBITS 6 TO 25 TO DECLARATION OF STEVEN N. FELDMAN IN SUPPORT OF PLAINTIFF MONSTER ENERGY COMPANY'S MOTION FOR A PRELIMINARY INJUNCTION

Monster Energy Company v. Vital Pharmaceuticals, Inc.

Case No. 5:18-cv-1882-JGB-SHK

Monster Energy Company's Exhibits to Declaration of Steven N. Feldman ISO Motion for Preliminary Injunction

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EXHIBIT 6

bangenergy.ceo • Follow

bangenergy.ceo When in doubt block them out. In life when they tell you there's no shelf space -- make your own shelf space! When multibillion-dollar competitors pay for space retaliate with a vengeance. Thank all of you for your awesome support in making us the number one brand of of key workout influencers!

162w

alexi_gabrielle_ 💥💥

162w Reply

princessraysa #VPXFamily

162w Reply

85 likes

FEBRUARY 29, 2016

Add a comment...

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EXHIBIT 7

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(https://bang-energy.com)

PRODUCTS APPAREL (HTTPS://BANG-ENERGY.COM/PRODUCT-CATEGORY/APPAREL/)
MEDIA & EVENTS COMPANY ACCOUNT (HTTPS://BANG-ENERGY.COM/MY-ACCOUNT/)
CONTACT US (HTTPS://BANG-ENERGY.COM/CONTACT-US/)

About Us

ABOUT US

My name is **Jack Owoc, CEO, CSO (Chief Scientific Officer) and founder of Bang Energy**, established in 1993. My elite team and I run Bang Energy, VPX and Redline with the same passion, energy and enthusiasm as I did 24 years ago. Sleeping on an air mattress on the floor in order to vigorously pursue my destiny and dreams sounds crazy, but this small sacrifice was worth the massive rewards and magnificent blessings that flowed through me onto millions of others just like you.

My objective from the very beginning was to intentionally help others. I knew in my heart that the more people I helped, the more successful and prosperous Bang Energy would become. My mission statement was simple, to make the highest quality nutritional supplements on the market, backed by scientific research. I felt obligated to start my own supplement company and set the highest standards in manufacturing because I was tired of all the lies and deception that unscrupulous supplement companies were using to purposefully rip off consumers. I intended to hold myself and the company to a higher standard than any other company on the planet. In fact, I wanted to run Bang Energy like a pharmaceutical company and adhere closer to their higher standards. This is precisely why the acronym VP(X) actually stands for Vital Pharmaceuticals with the X appearing lower than VP similar to how it appears in RX.

FROM THE BLACK BOARD TO THE BOARD ROOM

Earlier in my career, I was a high school science teacher. I taught six different Science disciplines, along with English, Health and ran Internal Suspension over a period of nine years. During this time, I also developed whole food eating strategies and combined them with vigorous training programs for both men and women who wanted to get into peak physical condition. The thing that set me apart from others who were also doing this was that I based everything off of science and made supplementation an integral part of my protocol. The results my clients achieved far exceeded other trainers and/or diet coaches. The results achieved with the addition of science and supplements always kept my clientele on top!

I kept meticulous details on the alternating macro-nutrient profiles of all my clients never once counting or paying attention to calories. However, something strange happened one month where a select group of my clients did not lose any body fat. This was shocking since all my clients were performing vigorous exercise and following their whole food nutrition and supplement program. Nevertheless, my clients' progress had come to a screeching halt one month! Compare this to the average client who consistently dropped four percent body fat per month.

Keeping with sound scientific principles – I immediately identified the changed variable. The only variable that changed with the group that was not losing body fat was the substitution of a different egg protein supplement. This was important because this egg protein supplement was consumed twice per day. Remember, this was the early 90's, and egg white protein was the only protein supplement on the market at that time. I had an uneasy feeling about this egg protein, so I sent it out to a lab to be tested. The protein assay returned from the lab was unbelievable; results showed that it was 90 percent maltodextrin, along with some ash and moisture, and contained no protein whatsoever! Knowing that I had recommended a protein supplement to my clients that was complete garbage that had impeded their results made me furious!

Things went from bad to worse. Shortly thereafter, my best friend was playing professional basketball. He was HIGHLY allergic to milk protein. With all the trust in the world, my best friend asked me to recommend the purest egg protein and send it to him. I sent him Med Sport Egg Protein. Upon consuming this protein, he asphyxiated in the shower. Suffocating and near death he pounded on the shower doors. His wife rescued him and immediately transported him to the hospital where the medical staff saved his life. The irony of this grand deception ran deep – who would have known that my friend would need to be saved by a medical staff from using a product called, Med Sport?

Enraged with anger at the corruption, dishonesty and utter tomfoolery in the supplement industry, set me on an unwavering warpath. First I exposed these supplement companies in the media and one of them actually shut its doors and went out of business. Then I took decisive action using intensive scientific research and development to innovate and create supplements that yielded extreme efficacy and impeccable purity – to create a sports and performance nutrition company that tested and set the highest standards for quality. I declared and committed to deliver SUPER PREMIUM quality sports and performance nutrition products backed by evidence-based scientific research. This is why testing and studies are nonstop at VPX/Bang/Redline headquarters to bring to market the most cutting-edge muscle, performance, and appearance-enhancing supplements possible.

SUPPLEMENT SCAMS COSTING YOU MONEY AND MUSCLE!

As previously mentioned, one of the reasons I entered into the supplement industry was my disgust for unscrupulous supplement manufacturers who were intentionally mislabeling their supplements and ripping the public off. However, let's be crystal clear; my broader vision was to create supplements that were super potent

and highly effective – supplements so effective that they had the power to positively impact lives and radically improve health in a very short period of time.

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Surprisingly, supplements aren't much better today than they were 24 years ago. Almost every single sports nutrition company offers a worthless, muscle-destroying pre-workout called a "concentrate". It is a rigged system where the health food or online store collaborate to push a concentrate on you because of the massive profit that they make at your expense! You lose both money and muscle, while they profit handsomely. It is not just the small companies either that are ripping you off. One of the biggest protein manufacturers in the world was recently tested to be 30% under protein claimed on the label and also contained 30% of what I refer to as "non-protein filler". Compare that to our **SRO™ Zero Carb® Protein** which contains the highest protein content per pound and per ounce! Further scams are evident by the largest seller of ready to drink protein beverages that tested 32% under label claim. This is insane my friends. There is a willful and purposeful intent to rip you off. Worse yet, you have to wonder what the hell is in these products that you are drinking that isn't protein!

QUALITY CONTROL: TRUTH IN LABELING

This is why Bang Energy does things differently! All of our raw materials are received into the warehouse, quarantined, and then tested for efficacy in our own state of the art laboratories to ensure that we only provide the end-consumer with the best product possible. Raw materials are sampled and taken to the quality control lab for analysis. Our analysis of each ingredient is conducted by tests on several levels; first through our high-performance liquid chromatography (HPLC) units that confirm the identity and purity levels of the ingredient; and second, the physical characteristics of the compound are verified through our infrared spectroscopy (IR) machine. Once the test results meet our set release specifications and the supplier's certificate of analysis, the ingredient is released and can be utilized within manufacturing. Maintaining this high level of testing ensures that every Bang Energy product is manufactured to its intended design and that we continually produce products that meet and exceed our customers' expectations.

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THE FRONT RUNNER IN SPORTS NUTRITION

One of the most prestigious accomplishments Bang Energy has achieved is that we have more university proven double-blind placebo-controlled sports and performance nutrition studies on our finished products than all the supplement companies in our industry combined! We don't engage in unethical and deceptive advertising practices by bloviating that users gained 10 pounds on a "key Muscle building compound" in our product or lost 22 pounds of fat with a "key fat burning ingredient" in our product. The companies that make these intellect-insulting claims conveniently never tell you what specific ingredient they are referring to. They also never tell you the exact amount used in their so called or research study. Nor, do the tell you how long you have to use this mysterious "key ingredient"! Worse yet, they don't use the real compound used in the study. Let's say for example, a specific herb containing 28% alkaloids or polyphenols was used in the study. They will use the "same herb by name only" but this worthless herb will be devoid of and active alkaloids or polyphenols. Frankly, they don't give a damn about you! They will list as many as 50 compounds on the label sprinkled in their products is worthless pixie dust amounts.

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> *"This is why Bang Energy conducts university double-blind placebo-controlled sports and performance nutrition studies on our FINISHED PRODUCTS – we sell you the exact products and exact ingredients with exact ingredient amounts that were used and proven effective at the most prestigious research universities in the world!"*

– Jack Owoc CEO, CSO Bang Energy

Given the distinction, "The Frontrunner in Sports Nutrition" Bang Energy continues to utilize intense research to develop the world's most effective muscle, appearance and performance-enhancing supplementation, beverages and nutrition.

> *"The science and the ability to create superior products is something we take ownership of and take very seriously. Bang Energy Sports has funded 22+ landmark sports nutrition studies at the country's top universities such as, UCLA, Florida State, Baylor, Southern Maine, University of Tampa, College of Pittsburgh, Memphis University and many others. As a result of these studies, VPX Redline has successfully developed and produced a full line of university proven nutritional supplements and performance beverages. As of now, there are at least a dozen studies that have been published or are in progress. Bang Energy has product-specific studies on 6 Meltdown Studies, Redline Xtreme, Redline Princess, Zero Carb Protein, Protein Rush, NO-Shotgun, two NO-Shotgun/NO-Synthesize Stack Stuides and is in the process of conducting a bleeding edge study with Division I collegiate athletes that will be released in the coming months! No company has a dedication and commitment to science like VPX! A test of Meltdown Fat Assault RTD drink performed at the College of New Jersey, Ewing, N.J., showed a 14 percent increase in metabolism for more than three hours per 4-ounce serving. A College of New Jersey study found that 4-ounces of Redline Xtreme provided a 7.5 percent improvement in reaction time, 13 percent increase in energy and 15 percent increase in focus.Our Pre-Workout SHOTGUN 5X research found that subject's experienced a mind-blowing 148.65% increase in muscle DNA and up to a 5-fold increase in muscle gene proteins! The mind-blowing message here is that we created products that actually induce nutria-genomics which means positively altering muscle genes through supplementation! We are on fire right now and I personally 2017 will bring you innovations that will rock your fragile world!"*

– Jack Owoc CEO, CSO Bang Energy

BANG ENERGY TAKES THE SPORTS BEVERAGE WORLD BY STORM

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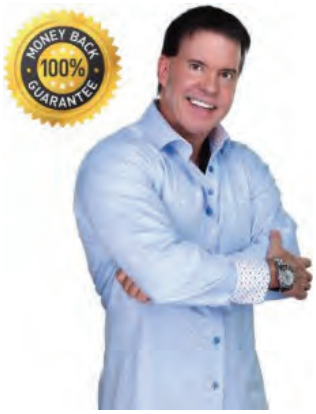
Initially we focused on sports nutrition supplements but have rapidly expanded into the ready-to-drink muscle building and performance-enhancing beverage market. Bang Energy beverages, such as **Redline Xtreme®, Protein Rush®, Bang® and Redline Black Diamond™** are designed to radically improve performance, increase muscle and improve appearance. VPX currently has a staff of 167 employees in its 102,000 square-foot facility where every aspect of its products are created – from research and development to manufacturing to sales and marketing. The results have continued to be successful — Bang Energy's beverages are now available in all 50 states through various distributors. In several states, its distributor network is vast, such as California which boasts a network of 15 direct store distributors as well as five in Texas and four in Georgia. Currently, its beverages can be found at many retailers, such as Quik Trip, 7-Eleven, Ralph's and Chevron outlets. Bang Energy products are also sold in 37 countries worldwide.



100 % MONEY BACK GUARANTEE

I am so confident in Bang Energy's products effectiveness that I guarantee them. Just use the products as instructed on the label for 30 days, while maintaining a sensible training regime and a healthy diet. If you are not satisfied with the results, please send the goods back to us in the original packaging within 30 days for a full refund.

– JACK OWOC CEO, CSO BANG ENERGY

EXHIBIT 8

Vital Pharmaceuticals, Inc. dba VPX Sports 4/24/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

WARNING LETTER

VIA OVERNIGHT DELIVERY
RETURN RECEIPT REQUESTED

APR 24 2015

Jack Owoc
Vital Pharmaceuticals
1600 North Park Drive
Weston, FL 33326

Re: 446357

Dear Mr. Owoc:

This letter concerns your products VPX Redline White Heat (strawberry, fruit punch, and watermelon) and MD2 Meltdown, which are labeled and/or offered for sale as dietary supplements. The Supplement Facts panel on your product labels declares 4-Amino-2-Methylpentane Citrate as a dietary ingredient. This ingredient is also called, among other names, 1,3-Dimethylbutylamine, DMBA, 2-amino-4-methylpentane, AMP citrate, and 4-methyl-2-pentanamine, and will be referred to in the rest of this letter as DMBA.

The term “dietary supplement” is defined in section 201(ff) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(ff)). Given that you have declared DMBA as a dietary ingredient in the labeling of your product, we assume you have a basis to conclude that DMBA is a “dietary ingredient” under section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)). Assuming that DMBA is a “dietary ingredient,” it would also be a “new dietary ingredient” for which a notification is required under section 413(a)(2) of the Act (21 U.S.C. 350b(a)(2)) and 21 CFR 190.6.

Under section 413 of the Act (21 U.S.C. 350b), a dietary supplement that contains a new dietary ingredient (i.e., a dietary ingredient not marketed in the United States before October 15, 1994) shall be deemed adulterated under section 402(f) of the Act (21 U.S.C. 342(f)) unless it meets one of two requirements:

1. The dietary supplement contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or
2. There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

To the best of FDA's knowledge, there is no information demonstrating that DMBA was lawfully marketed as a dietary ingredient in the United States before October 15, 1994, nor is there information demonstrating that this ingredient has been present in the food supply as an article used for human food in a form in which the food has not been chemically altered. In the absence of such information, DMBA is subject to the notification requirement in section 413(a)(2) of the Act (21 U.S.C. 350b(a)(2)) and 21 CFR 190.6. Because the required notification has not been submitted, your product is adulterated under sections 402(f)(1)(B) and 413(a) of the Act (21 U.S.C. 342(f)(1)(B) and 350b(a)).

Even if the required notification had been submitted, we know of no evidence that would establish that your products are not adulterated. In the absence of a history of use or other evidence of safety establishing that DMBA, when used under the conditions recommended or suggested in the labeling of your products, will reasonably be expected to be safe, VPX Redline White Heat (strawberry, fruit punch, and watermelon) and MD2 Meltdown are adulterated under sections 402(f)(1)(B) and 413(a) of the Act (21 U.S.C. 342(f)(1)(B) and 350b(a)) because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under sections 301(a) and (v) of the Act (21 U.S.C. 331(a) and (v)). To the best of FDA's knowledge, there is no history of use or other evidence of safety establishing that DMBA will reasonably be expected to be safe when used as a dietary ingredient.

It has come to our attention that DMBA used in products in the dietary supplement marketplace may be produced synthetically. Section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)) defines "dietary ingredient" as a vitamin, mineral, amino acid, herb or other botanical, or dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract or combination of any dietary ingredient from the preceding categories. Synthetically produced DMBA is not a vitamin, mineral, amino acid, herb or other botanical. To the best of FDA's knowledge, synthetically produced DMBA is not commonly used as human food or drink. Further, synthetically produced DMBA is not a concentrate, metabolite, constituent, extract or combination of the preceding categories. Therefore, synthetically produced DMBA is not a dietary ingredient as defined in section 201(ff)(1) of the Act.

We request that you take prompt action to correct the violations cited above, as well as any other violations associated with your VPX Redline White Heat (strawberry, fruit punch, and watermelon) and MD2 Meltdown products or other dietary supplement products marketed by your firm, including any that contain DMBA. We also remind you that the new dietary ingredient notification requirement applies to all dietary supplements that contain new dietary ingredients that have not been present in the food supply as articles used for food in a form in which the food has not been chemically altered. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations.

Failure to immediately cease distribution of your products VPX Redline White Heat (strawberry, fruit punch, and watermelon), MD2 Meltdown, and any other products you market that contain DMBA could result in enforcement

action by FDA without further notice. Sections 302 and 304 of the Act provide for seizure of violative products and injunction against the manufacturers and distributors of violative products [21 U.S.C. §§ 332 and 334].

We request that you advise us in writing, within 15 days of receipt of this letter, as to the specific steps that have been or will be taken to correct these violations, including any steps taken with respect to product currently in the marketplace. Your response should also include an explanation of each step taken to ensure that similar violations do not recur, as well as documentation to support your response. Your written reply should be directed to Mr. Rob Genzel Jr., United States Food and Drug Administration, Center for Food Safety and Applied Nutrition, 5100 Paint Branch Parkway, Office of Compliance (HFS-608), Division of Enforcement, College Park, Maryland 20740-3835. If you have any questions, please contact Mr. Genzel at **rob.genzel@fda.hhs.gov (mailto:rob.genzel@fda.hhs.gov)**.

Sincerely,
/s/
William A. Correll
Director
Office of Compliance
Center for Food Safety and Applied Nutrition

Cc:
15751 SW. 41st Street
Suite 300
Davie, FL 33331

Close Out Letter

- **Vital Pharmaceuticals, Inc. dba VPX Sports - Close Out Letter 4/3/17 (/ICECI/EnforcementActions/WarningLetters/2015/ucm551332.htm)**

More in Warning Letters (/ICECI/EnforcementActions/WarningLetters/default.htm)

EXHIBIT 9

Beef Up Your Muscles and Your Brain with Super Creatine

Nootropics are popular amongst college students; unfortunately, many students will resort to sugary, caffeinated beverages to help with studying. What if there was a supplement that makes you smarter, gives you a greater attention span, and improves your memory? Well,

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What Is A Healthy Snack? via Bobo's

Europa Customer Feature – American

there is – and it's creatine. Everyone knows creatine is a great muscle builder and can increase athletic performance, but new research suggests that creatine can increase your mental function, as well. Your brain is a muscle, which stores creatine just like your skeletal muscle does. With that being said, your brain can fatigue just like your muscles can when exercising.

FUN FACT: Your brain makes up about 1-3 percent of your body weight. Billions of neurons in our brains use 20 percent of our body's total ATP-derived energy.

Creatine is no longer just for athletes. Anyone looking to improve mental performance in school, and even in sports, should be consuming creatine.

Here are a few things creatine has been backed up by research to do:

- Be neuroprotective in the brain
- Increases cognition
- Increases attention span
- Delays mental fatigue
- Has anti-depressive effects
- Has antioxidant effects in the brain

Research has found that brain creatine is much harder to increase than skeletal muscle. This means that creatine gets taken up readily by your muscles, but not by your brain because of the blood-brain barrier.

What is the Blood-Brain Barrier?

The blood-brain barrier is semi-permeable. This means that it allows some materials to cross, but prevents others from crossing. Some of the notable effects of the BBB are:

Nutrition Center, Everett, MA

Celebrating Our Top Sales Consultants of 2018

The Golden Age of Strength & Conditioning: The Chip Sigmon Story

Highlights from the Arnold 2019 After-School All-Stars Charity Event

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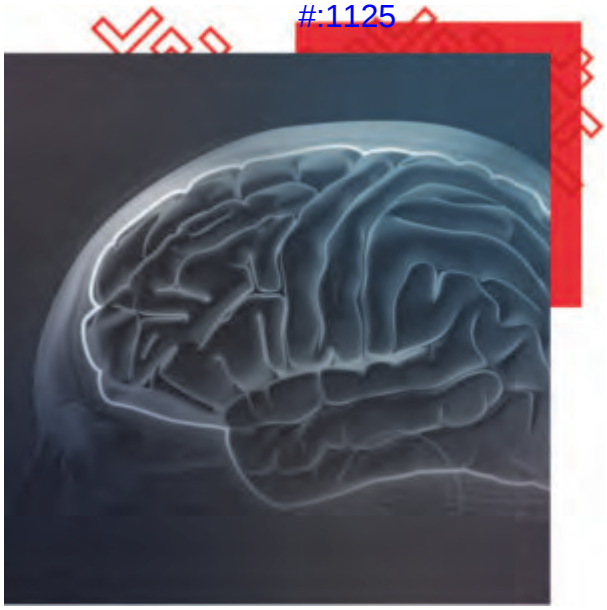
Supplementation

- Protects the brain from “foreign substances”
- Compounds that are very small and/or fat-soluble pass freely across the BBB



FUN FACT: Alcohol, cocaine, and caffeine pass freely across the BBB. Therefore, certain substances have effects almost immediately because they’re readily crossing the BBB, whereas other substances don’t.

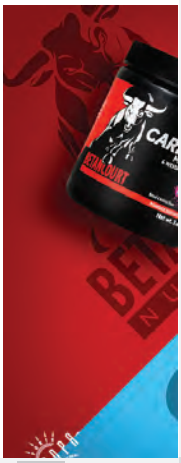
Creatine does not get absorbed by the brain sufficiently because it has trouble crossing the BBB. A recent study highlights how poorly creatine is absorbed in the brain, especially when considering the aging process. The decline in brain creatine may be related to cognitive decline in the elderly.

A new study examined the impact of age, diet, tissue with creatine supplementation. Participants received .3 grams of creatine monohydrate per kg of body weight for seven days. This is a typical creatine loading phase that most researchers use to saturate the body with creatine. In addition to muscle, they also use MRI to examine how much creatine was taken up in the brain. Researchers found that:

- Muscle creatine increased in all groups
- Diet influenced muscle creatine, but did not impact brain creatine

Training

Uncategorized



- Brain creatine remained unchanged after creatine loading
- Brain creatine content was found to be lower than muscle creatine regardless of age or diet

This study suggests that it's much harder to get creatine across the blood-brain barrier than into muscle. It also shows that brain creatine levels decrease with aging which may account for an age-related decline in mental function. Remember, your brain requires creatine to work, just like muscle does. A concerning fact of the study was that brain creatine did not change, which means you must take a highly bioavailable creatine, such as Super Creatine. The Super Creatine peptide found in Bang Energy is much more bioavailable than regular creatine, and has added neurotrophic, such as caffeine and CoQ10. Bang Energy is the perfect mental enhancement drink for college students with its patented Super Creatine, CoQ10, caffeine, and BCAAs.

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Call | 1.800.447.4795
E-mail | Info@EuropaSports.com

Europa Charlotte (Headquarters)
11401 Granite Street
Charlotte, North Carolina
28273

EXHIBIT 10


SUPER CREATINE
bang
POTENT BRAIN AND BODY FUEL
PEACH MANGO
Natural Flavors
16 fl oz (1 PT) 473 mL
0
CALORIES PER CAN


BCAA AMINOS
bang
POTENT BRAIN AND BODY FUEL
BY THE MAKERS OF THE LEGENDARY
REDLINE® ENERGY PRODUCTS
Make no Mistake - BANG® is not your stereotypical high sugar, life-sucking soda masquerading as an energy drink! High sugar drinks spike blood sugar producing metabolic mayhem causing you to crash harder than a test dummy into a brick wall. Power up with BANG's potent brain & body-rocking fuel: Creatine, Caffeine, CoQ10 & BCAAs (Branched Chain Amino Acids).
Life is an Xtreme Sport and BANG® is the Xtreme Energy source to Live Life Xtreme!
Not intended for individuals under the age of 18
Made in USA from Domestic and Imported Ingredients
PATENT 8,445,456
0g TOTAL CARBS PER CAN
0 SUGARS PER CAN
0 CALORIES PER CAN
0 ARTIFICIAL COLORS
CAUTION: Do not use this product if you are pregnant or nursing. Do not consume this product if you are taking any prescription drug and/or have any medical condition. The user of this product assumes all liability if this product is used in a manner not consistent with label guidelines.
This product contains caffeine and should not be used with any other caffeine containing products. This product is intended for use by healthy individuals only.
†At the time of manufacturing, some vitamins are likely to degrade.
PLEASE RECYCLE
©2018 VITAL PHARMACEUTICALS, INC. ALL RIGHTS RESERVED.
To report a serious adverse event or obtain product information, contact 1600 North Park Drive, Weston, FL 33326 USA • (954) 641-0570
VPXSPORTS.COM


ULTRA COQ10
CONTAINS NO FRUIT JUICE
Nutrition Facts
Serving Size 1 Can (16 fl oz [473 mL])
Amount Per Serving
Calories 0
Calories from Fat 0
% Daily Value*
Total Fat 0 g 0%
Saturated Fat 0 g 0%
Trans Fat 0 g
Cholesterol 0 mg 0%
Sodium 40 mg 2%
Potassium 85 mg 2%
Total Carbohydrate 0 g 0%
Dietary Fiber 0 g 0%
Sugars 0 g
Protein 0 g
Vitamin C 50%† • Niacin 25%†
Vitamin B6 25%† • Vitamin B12 25%†
Magnesium 2%†
*Percent Daily Values are based on a 2,000 calorie diet.
† Not a significant source of vitamin A, calcium and iron.
Stable Aqueous Amide-Protected Bioactive Creatine Species - U.S. Patent No. 8,445,466
INGREDIENTS: Carbonated water, citric acid anhydrous, caffeine anhydrous, sodium benzoate (preserves freshness), potassium citrate monohydrate, sucralose, natural flavors, L-Leucine, potassium phosphate dibasic, vitamin C (ascorbic acid), acesulfame potassium, potassium sorbate (preserves freshness), magnesium chloride, SUPER CREATINE® (Creatyl-L-Leucine [Creatine bonded to L-Leucine]), L-isoleucine, L-valine, calcium chloride, calcium disodium EDTA, vitamin B3 (niacinamide), CoQ10 (coenzyme Q10), vitamin B6 (pyridoxine hydrochloride), and vitamin B12 (methylcobalamin).
Warning: Too much caffeine may cause nervousness, irritability, sleeplessness, and occasionally, rapid heartbeat. Not recommended for use by individuals under 18 years of age. One serving of BANG® provides 300 mg of caffeine which is more than two cups of coffee.
BEST BY DATE AT BOTTOM
0 CALORIES PER CAN

EXHIBIT 11

Energy drink first to add creatine

With more caffeine than three cups of coffee and its water-soluble super creatine, Bang is invading the lives of those looking for a quick caffeine fix and a way to improve focus.

Lauryn Stornelli

Emma Bauer (https://cactusshadowscspress.com/staff/?writer=Emma%20Bauer)

Keagan Neff, a sophomore, has hopped on

board with this new energy drink.

(https://cactusshadowscspress.com/staff/?writer=Lauryn%20Stornelli), creeker editor
November 29, 2018

 (https://cactusshadowscspress.com/health/2018/11/29/energy-drink-first-to-add-creatine/#respond)  (https://www.facebook.com/sharer/sharer.php?u=https%3A%2F%2Fcactusshadowscspress.com%2Fhealth%2F2018%2F11%2F29%2Fenergy-drink-first-to-add-creatine%2F)  (https://twitter.com/intent/tweet?text=Energy+drink+first+to+add+creatine&url=https%3A%2F%2Fcactusshadowscspress.c

Bang energy drinks are finding their place in the daily routines of people all around the nation, but not without some backlash. The big concern of the drink that seems to be going straight over the average consumer's head is the question of what actually is in the drink and why is it so much stronger than most energy drinks.

In 2012, CEO of VPX, Jack Owoc wished to introduce a new wave of energy drinks to the public eye that would promote human health, rather than destroy it.

"Bang contains my patented creatine-amino acid peptide which is the world's only water-stable creatine," explained Owoc.

Super Creatine

Creatine is a supplement that is meant to help muscles produce energy during heavy lifting or high-intensity exercise. This means that the energy spike that a person experiences solely relies on the amount of physical activity that they pursue.

"I like just drinking it before the gym because it's really good for pre-workout, but I wouldn't drink it if I wasn't planning on exercising," said Brooke Barrett, a senior.

However, the creatine that is in Bang is known as "super creatine," an ingredient named, patented, and virtually invented by Owoc. It separates itself from regular creatine because it is the world's only soluble creatine. Though, the difference between the two goes deeper than that.

Studies on creatine have shown it can increase your mental

function as well as athletic. Super creatine differs from the norm, because it has a fatty acid chain (https://en.wikipedia.org/wiki/Fatty_acid) that makes it easier to cross the blood brain barrier (https://en.wikipedia.org/wiki/Blood%E2%80%93brain_barrier). The blood brain barrier, which is semipermeable, allows certain materials through to the brain but blocks others. While regular creatine can enhance athletic performance, it tends to cut off before having effects on the brain.

Focus

“The focus of the super creatine is not for muscle function, but for cognition. By combining this form of creatine with caffeine, it works synergistically for mental focus,” said Owoc.

Essentially, Owoc is paving a way for anyone who is struggling with low counts of energy, whether that’s cognitive or physical, leaving room for high demand in a non-competitive market.

The benefits of regular creatine are offered to more than just athletes at the cost of consuming a drink with various flavors and almost immediate results.

“I would take creatine pills and have to wait a whole hour before I could work out and this is just right away, I can just drink it,” Derek Hertzell, a senior.

Hertzell, who averagely drinks three Bangs a week, is not the only one who consumes this drink regularly. The drinks can be spotted lurking around the campus, especially in recent weeks.

The good and the bad

It is arguable whether or not a person should be ingesting such a large amount of caffeine and creatine. According to a review published by GreenEyedGuide, an average adult should not be consuming more than 400mg of caffeine in one day and no more than 200mg in one sitting, all while Bang has a total of 300mg in one can. Another concern is the warning label on the can that says the drink is not intended for consumers under 18.

Recently, there was a lawsuit on VPX Sports for false advertisement, which boiled down to the drinks having an insignificant amount of branched-chain amino acids and CoQ10 compared to what the company was boasting. Both of those

ingredients are supposed to increase athletic performance.

Leave a Comment

EXHIBIT 12

bangenergy.ceo • Follow

bangenergy.ceo ENERGY. MUSCLE. PERFORMANCE! @estefaniaserrano @almafitness @theladypanthers @mstriciasfl

290w

genske Love #bang need it in Michaels @body_scenes in boca raton - all @vpx_sports products!!

290w Reply

dstock_family @genske reach out to us. My email is in my profile we will get you going.

290w Reply

38 likes

SEPTEMBER 12, 2013

Add a comment...

049

EXHIBIT 13

bangenergy.ceo • Follow

bangenergy.ceo GOLDEN BROWN & MUSCLE BOUND! #AllBangedUp in #Miami @megliz.swim @bangenergy #IceColdCreatine.
Most people think of creatine for muscles, Creatine is also critical for optimal brain function. In fact, vegetarians don't get enough creatinine the diet because they don't consume animal proteins. Consequently when they were given creatine, their IQ scores increased dramatically!.

204w

kattiavane Love it!

204w Reply

73 likes

MAY 9, 2015

Add a comment...

051

EXHIBIT 14


bangenergy.ceo • Follow
bangenergy.ceo Shots fired. Playas get all Banged up with Bang Energy Drink containing ICE COLD CREATINE! @stephhannah94 @redlineenergy @vpx_sports @vpxswimwear
264w
zamayracenteno 😍😍 love this!
264w Reply
laurenhealyy This is perfect OMG 😍😍💙❤️
264w Reply
megliz.owoc This was the cutest EVER! 😍😍@jennyhannah
47 likes
MARCH 16, 2014
Add a comment...
053

EXHIBIT 15

bangenergy.ceo • Follow

bangenergy.ceo #AllBangedUp on #IceColdCreatine @bangenergy Make no mistake – BANG is not your stereotypical high sugar, life-sucking soda masquerading as an energy drink! High sugar drinks spike blood sugar producing metabolic mayham causing you to crash harder than a test dummy into a brick wall. Power up with BANG's potent brain and body-rocking fuel: Creatine, Caffeine CoQ10 and BCAAs!
Life is an Xtreme Sport and BANG is the extreme energy source to live life Xtreme! @vpx_sports

192w

gorilladan @vpxredlineceo when

52 likes

JULY 28, 2015

Add a comment...

EXHIBIT 16

US008445466B2

(12) **United States Patent**
Owoc

(10) **Patent No.: US 8,445,466 B2**
(45) **Date of Patent: May 21, 2013**

(54) **STABLE AQUEOUS COMPOSITIONS COMPRISING AMIDE-PROTECTED BIOACTIVE CREATINE SPECIES AND USES THEREOF**

(76) Inventor: **John H. Owoc**, Weston, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 339 days.

(21) Appl. No.: **12/756,686**

(22) Filed: **Apr. 8, 2010**

(65) **Prior Publication Data**

US 2011/0251280 A1 Oct. 13, 2011

(51) **Int. Cl.**
A01N 33/26 (2006.01)

(52) **U.S. Cl.**
USPC **514/150**; 514/151

(58) **Field of Classification Search**
USPC 514/150, 151
See application file for complete search history.

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Primary Examiner — Renee Claytor
(74) *Attorney, Agent, or Firm* — Saliwanchik, Lloyd & Eisenschenk

(57) **ABSTRACT**

The present invention provides amide-protected creatine molecules and compositions, containing one or more bioactive forms of creatine in aqueous compositions, wherein bioactive forms of creatine do not appreciably degrade into creatinine. Also provided are various beneficial effects of administering aqueous compositions having at least one amide-protected creatine molecule.

12 Claims, No Drawings

STABLE AQUEOUS COMPOSITIONS COMPRISING AMIDE-PROTECTED BIOACTIVE CREATINE SPECIES AND USES THEREOF

TECHNICAL FIELD

This invention relates generally to stable aqueous solutions of creatine, methods for their preparation and methods of use.

BACKGROUND OF THE INVENTION

Many nutritional supplements are available at various retail outlets, in many forms, including tablets, pills, powders, and liquids intended for human consumption.

One nutritional supplement that has become popular is creatine, whose IUPAC name is 2-(carbamimidoyl-methyl-amino) acetic acid (CAS No. 57-00-1). Creatine occurs naturally in muscle and is believed to be an essential component in energy-producing metabolism and normal muscle function and growth. It is also believed by many to be useful to body-builders for increasing muscle mass, i.e., muscle-building.

Creatine supplementation offers a variety of health benefits. Studies have shown that creatine enhances athletic performance in the strength-power sports, promotes gains in lean body mass and muscle fiber hypertrophy (growth), improves neuromuscular function, especially in patients with metabolic diseases and decreased muscular fitness, and improves neural function and cognitive abilities. In addition, no adverse health effect has been observed in both short- or long-term creatine supplementations. In a thorough scientific review published in the Journal of Strength and Conditioning, scientists summarized 22 published studies, and concluded that the average increase in muscle strength following creatine supplementation during resistance training was 8% greater than the average increase in muscle strength following placebo ingestion during resistance training (20% vs. 12%). Also, the average increase in weightlifting performance (maximal repetitions at a given percent of maximal strength) following creatine supplementation during resistance training was 14% greater than the average increase in weightlifting performance following placebo ingestion during resistance training (26% vs. 12%). In addition, creatine supplementation improves the bench press 1-Rep Max (RM) performance of 3% to 45%, and the weightlifting performance in the bench press of 16% to 43%.(1)

In addition, scientists tested the hypothesis whether oral creatine supplementation 5 grams daily for six weeks would enhance intelligence test scores and working memory performance in 45 young adult, vegetarian subjects in a double-blind, placebo-controlled, cross-over design. The results showed that creatine supplementation significantly improves both working memory (backward digit span) and intelligence (Raven's Advanced Progressive Matrices).(2)

Furthermore, creatine supplementation has neuroprotective effects, useful for preventing and treating neurological diseases such as Huntington's disease, Parkinson's disease, or amyotrophic lateral sclerosis.(3) One investigation found that 5 grams of creatine supplementation daily, coupled with resistance training (3× per week for 15 weeks), improved physical function in a 26-year-old man with myasthenia gravis. This individual had a 7% increase in body weight, 4% increase in fat free mass, and improved peak strength up to 37%. (4) Another investigation found that creatine supplementation improves skeletal muscle function in patients with McArdle disease.(5)

In addition, creatine supplementation significantly enhances muscular fitness of patients with Parkinson disease (PD), who exhibit decreased muscular fitness, including decreased muscle mass, muscle strength, and increased fatigability. Twenty patients with idiopathic PD were randomized to receive creatine monohydrate supplementation during resistance training (CRE) or placebo (lactose monohydrate) during resistance training (PLA), using a double-blind procedure. Both the creatine and placebo supplementation consisted of 20 g/d for the first 5 days and 5 g/d thereafter. Both groups participated in progressive resistance training (24 sessions, 2 times per week, 1 set of 8-12 repetitions, 9 exercises). Creatine supplementation significantly improved chest press strength and biceps curl strength.(7)

There are also data concerning the short and long-term therapeutic benefits of creatine supplementation in children and adults with gyrate atrophy (a result of the inborn error of metabolism with ornithine delta-aminotransferase activity), muscular dystrophy (facioscapulohumeral dystrophy, Becker dystrophy, Duchenne dystrophy and sarcoglycan deficient limb girdle muscular dystrophy), McArdle's disease, Huntington's disease and mitochondria-related diseases. Hypoxia and energy related brain pathologies (brain trauma, cerebral ischemia, prematurity) could benefit from Cr supplementation.(12) Creatine supplementation has also been shown to lead to an improvement in various cognitive tasks.(13)

More beneficially, there is no scientific evidence that the short- or long-term use of creatine monohydrate has any detrimental effects on otherwise healthy individuals. In fact, five days of creatine supplementation enhances the dynamic strength and may increase anaerobic metabolism in the lower extremity muscles, and improves performance in consecutive maximal swims in highly trained adolescent (mean age 16) fin swimmers.(11)

No adverse effects on renal function has been observed in short term (5 days), medium term (9 weeks) and long term (up to 5 years) oral creatine supplementation in small cohorts of athletes.(8) Another investigation examined over a 21-month period, 98 Division IA college football players who consumed in an open label manner creatine or non-creatine containing supplements following training sessions. Subjects who ingested creatine were administered 15.75 g/day of creatine monohydrate for five days and an average of 5 g/day thereafter in 5-10 g/day doses. No adverse effect has been observed in long-term creatine supplementation (up to 21-months).(9)

According to the position stand published by the International Society of Sports Nutrition(10), creatine is the most effective ergogenic nutritional supplement currently available to athletes in terms of increasing high-intensity exercise capacity and lean body mass during training. Also, supplementation is not only safe, but possibly beneficial in regard to preventing injury and/or management of select medical conditions when taken within recommended guidelines.

Despite its significant health benefits, creatine supplementation can only be offered in powder, pill or capsule form. Currently, no aqueous-based formulation containing appreciable amounts of creatine, intended for oral human consumption, is available in the marketplace. This is because creatine is unstable in aqueous systems, in which it rearranges to creatinine.

The rate of creatine degradation in aqueous systems can be determined based on serum creatinine concentration. Creatine is non-enzymatically converted into creatinine at approximately 1.7% daily in a typical 70 kg individual. The skeletal muscle represents the primary site of creatinine production.

Creatine is also degraded in the GI tract into creatinine at an estimated rate of 0.1 g of a 5 g dose per hour.

Creatinine has no nutritional benefits and does not enhance muscle fitness. Moreover, abnormal serum creatinine levels may be correlated with serious disease or renal dysfunction. For example, blood creatinine levels are used as a measure of renal function, and abnormally high levels indicate possible renal dysfunction.

Conditions leading to high blood creatinine levels further include blockage of the urinary tract (such as by a kidney stone), heart failure, dehydration, excessive blood loss that causes shock, gout, or muscle conditions (such as rhabdomyolysis, gigantism, acromegaly, myasthenia gravis, muscular dystrophy, and polymyositis). Usually a high blood creatinine level means that the creatinine clearance value is lower than normal.

There is a critical need in the art for a creatine composition that is stable in aqueous systems.

BRIEF SUMMARY

The subject invention provides stable aqueous compositions of at least one amide-protected, biologically-active form of creatine (creatyl-amide) molecule, wherein the carboxylic acid group of creatine is linked to, for example, an amino group of an amine, an amino acid or a peptide, thereby forming an amide bond. In a preferred embodiment, the compositions of the subject invention comprise:

a) at least one creatyl-amide species, wherein the carboxylic acid group of creatine is linked to an amino group of an amine, an amino acid or a peptide, thereby forming an amide bond; and

b) water.

In preferred embodiments, the stable aqueous compositions have a pH of about 1.5 to about 6.5, and contain creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine, and/or creatyl-beta-alanyl-1-methylhistidine.

Advantageously, these compositions are stable across a wide range of pHs and temperatures. These formulations are stable at temperatures between 4° C. (or less) and 40° C. (or higher). Advantageously, across this wide range of conditions, the concentration of bioactive species in these compositions does not decrease appreciably over periods of 40 or even 60 days or more.

The compositions of the subject invention may further comprise one or more additional materials selected from, for example, flavoring agents, colorants, viscosity modifiers, preservatives, fragrances, amino acids and their salts, vitamins, minerals, essential fatty acids, enzymes, co-enzymes, mono-glycerides, di-glycerides, tri-glyceride ester oils emulsifiers, hydrolyzed proteins, whey protein, stabilizers, flow modifiers, viscosity improvers, chelating agents, anti-oxidants, anti-microbials, benzoates, alcohols, esters of para-hydroxybenzoic acid, propionates, preservatives and surfactants.

The subject invention further provides methods for preparing and using these compositions. In preferred embodiments, the amide-protected creatine compositions can be formulated into nutritional supplements, aqueous and emulsion injectable formulations, aqueous clear gel systems, creams and lotions, active-in-adhesive transdermal systems, and aqueous liquid-reservoir transdermal patches.

The compositions of the subject invention can provide any one or more of a wide range of physiological benefits including, for example, regeneration of ADP to ATP in muscle tissue, increasing the serum concentration of creatine, increasing muscle fiber size/cross-sectional area and lean body mass, activating satellite cells, enhancing memory and cognitive function, enhancing the functional capacity of a mammal having a neuromuscular disease, increasing muscular strength, endurance and/or power, enhancing cognitive function in infants with inborn errors of creatine metabolism, and/or alleviating the deleterious effects of sleep deprivation.

DETAILED DESCRIPTION

The present invention provides amide-protected, biologically-active creatine (creatyl-amide) molecules and aqueous compositions containing these amide-protected creatine molecules. In preferred embodiments, the carboxylic acid group of creatine is linked to an amino group of an amine, an amino acid or a peptide, thereby forming an amide bond.

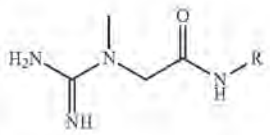
Advantageously, these amide-protected creatine molecules are stable in aqueous systems and suitable for administration to mammalian subjects. In a preferred embodiment, the stable aqueous compositions have a pH of about 1.5 to about 6.5, and the amide-protected creatine molecules are creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine, and/or creatyl-beta-alanyl-1-methylhistidine.

Further provided are methods of making and using these molecules and compositions.

Creatyl-Amide Compounds

In a first aspect, this invention provides amide-protected creatine molecules, wherein creatine is stabilized by protecting its carboxylic acid group. Creatine, as used herein, encompasses all biologically-active forms of creatine, and salts, derivatives and analogs thereof, including but not limited to, creatine monohydrate, disodium creatine phosphate tetrahydrate, and creatine hydrochloride.

In one embodiment, the general chemical formula of amide-protected creatine molecules of the subject invention is illustrated below, wherein the carboxylic acid group of creatine has been reacted with a molecule (R—NH) that contributes an amine group thereby forming the amide having the following formula:



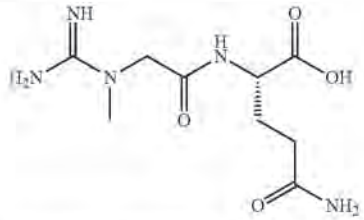
Preferably, the R—NH molecule that contributes the amine group is an amino acid or peptide.

The amide-protected creatine molecules, such as creatyl-L-glutamine and creatyl-L-leucine, are substantially stable in aqueous media. The covalent amide bond formed between creatine and the protecting group exhibits unexpectedly improved hydrolysis-stability.

Specifically, water alone is not sufficient to hydrolyze the amides. Rather, in addition to acid or basic conditions, the hydrolysis of the amide bond requires the presence of catalysts and/or prolonged heating.

In one embodiment, the carboxylic acid group of creatine is covalently linked to an amino acid molecule. In a specific embodiment, the carboxylic acid group of creatine is covalently linked to the amino group of glutamine and/or leucine.

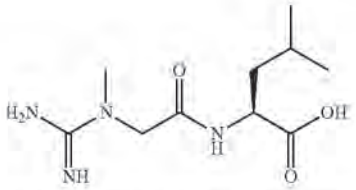
In a specific embodiment, the creatyl-amide molecule is creatyl-L-glutamine:



(I) Creatyl-L-Glutamine; IUPAC Name: 2s)-2-(2-carbamimidoyl-methyl-amino)acetamido)-4-aminocarbonyl-butanoic acid

Formula: $C_9H_{17}N_5O_4$
MW=259.26

In another specific embodiment, the creatyl-amide molecule is creatyl-L-leucine:



(II) Creatyl-L-Leucine; (2s)-2-(2-(carbamimidoyl-methyl-amino)acetamido)-4-methylpetanoic acid

Formula: $C_{10}H_{20}N_4O_3$
MW=244.29

In certain embodiments, creatine is protected with an amino acid selected from glutamine, leucine, arginine, histidine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, tyrosine, valine, alanine, asparagine, aspartate, cysteine, glutamate, glycine, proline, serine, and glutamic acid.

Preferably, creatine is protected with an L-amino acid selected from L-glutamine, L-leucine, L-arginine, L-histidine, L-isoleucine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-tyrosine, L-valine, L-alanine, L-asparagine, L-aspartate, L-cysteine, L-glutamate, glycine, L-proline, L-serine, and L-glutamic acid.

In another embodiment, creatine is stabilized by protecting the carboxylic group with a peptide. Useful peptides include, for example, di-peptides, tri-peptides, tetra-peptides, penta-peptides, and long-chain oligo-peptides. In certain embodiments, peptides useful for protecting creatine are composed of amino acids selected from the group consisting of glutamine, leucine, arginine, histidine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, tyrosine, valine, alanine, asparagine, aspartate, cysteine, glutamate, glycine, proline, serine, and glutamic acid. These peptides can be used to bond to creatine's carboxylic group, thereby forming an amide bond to stabilize creatine.

Preferably, the carboxylic acid group of creatine is protected by a natural amino acid molecule or a peptide composed of natural amino acids. In a further embodiment, creatine is stabilized by protecting the carboxylic group with a derivative of a natural amino acid or a peptide composed of natural amino acids, where any functional group of a side chain of the amino acid may be modified with one or more of the following groups, including but not limited to, alkyl, acyl, carboxyl, halo, carboxyl, carboalkoxy, carboxamide, haloalkyl, amino, alkylamino, hydroxy, hydroxyalkyl, and alkoxy of any length and structure.

In a preferred embodiment, the carboxylic group of creatine is protected by an amino acid derivative with similar structure-function to glutamine or leucine.

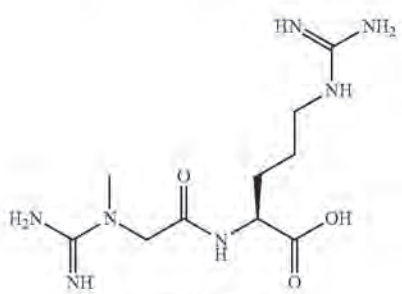
In certain embodiments, creatine is stabilized by protecting the carboxylic group with an amine, an amino acid, or a peptide, including but not limited to, natural amino acids; non-natural amino acids, such as for example, sarcosine, β-alanine, citrulline, ornithine, and prolinamide; hydroxylated amino acids, such as for example, 5-hydroxy lysine; dipeptides, such as for example, alanyl-L-glutamine; tripeptides; oligopeptides; and nutrient chemicals, such as for example, taurine, geranamine.

In a specific embodiment, creatine is stabilized by protecting the carboxylic group with carnosine (beta-alanyl-L-histidine), methylhistidine, or beta-alanyl methylhistidine.

Exemplified embodiments of creaty-amide molecules are shown below.

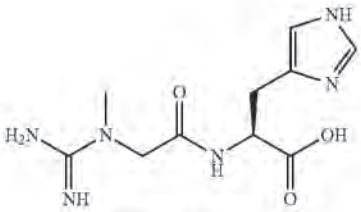
Creatyl-L-Essential Amino Acid Peptides

(III)



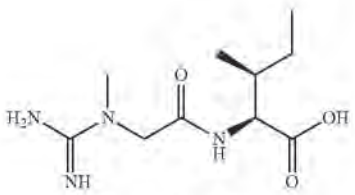
Creatyl-L-Arginine

(IV)



Creatyl-L-Histidine

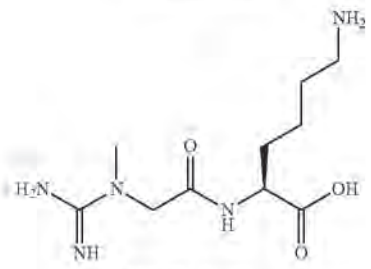
(V)



Creatyl-L-Isoleucine

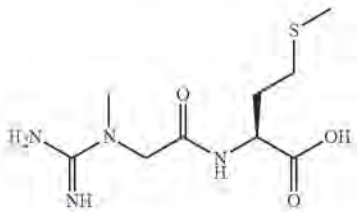
-continued

(VI)



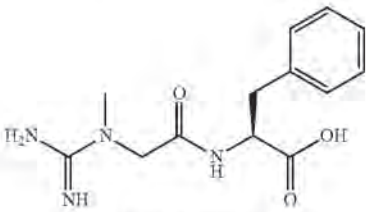
Creatyl-L-Lysine

(VII)



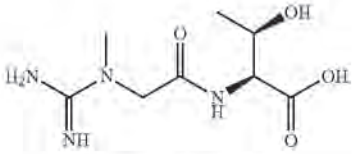
Creatyl-L-Methionine

(VIII)



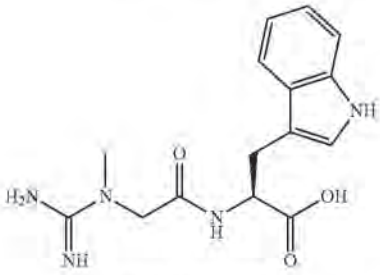
Creatyl-L-Phenylalanine

(IX)



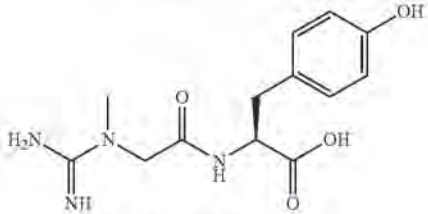
Creatyl-L-Threonine

(XI)



Creatyl-L-Tryptophan

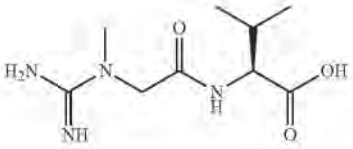
(XI)



Creatyl-L-Tyrosine

-continued

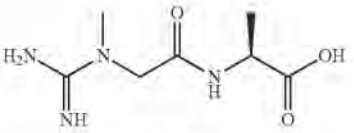
(XII)



Creatyl-L-Valine

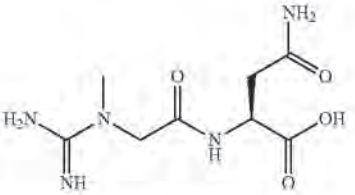
Creatyl-L-Unessential Amino Acid Peptides

(XIII)



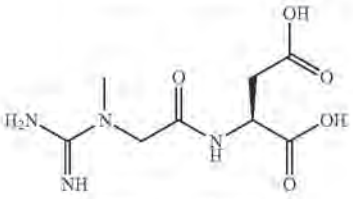
Creatyl-L-Alanine

(XIV)



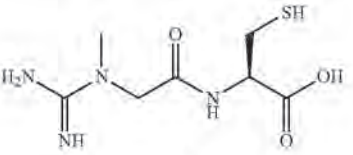
Creatyl-L-Asparagine

(XV)



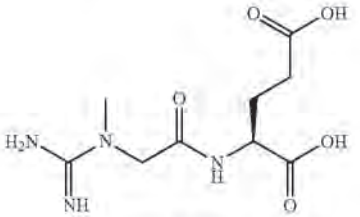
Creatyl-L-Aspartate

(XVI)



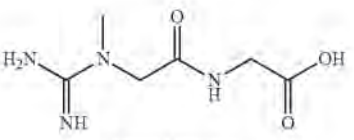
Creatyl-L-Cysteine

(XVII)



Creatyl-L-Glutamate

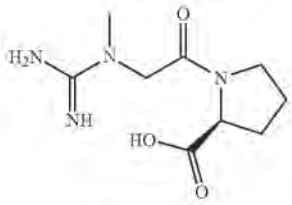
(XIII)



Creatyl Glycine

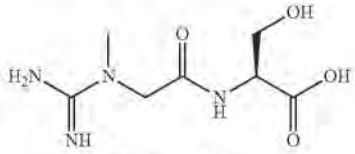
-continued

(XIX)



Creatyl-L-Proline

(XX)



Creatyl-L-Serine

The compounds of formulae (I) through (XX) above are all creatyl-amino acid species of the present invention.

Furthermore, this invention provides methods for synthesis of amide-protected creatine molecules.

To illustrate, creatyl-L-glutamine can be synthesized as follows. First, L-glutamine as the starting material is reacted with 2-chloroacetyl chloride to obtain N-chloroacetyl-L-Glutamine. This intermediate is converted to sarcosyl-L-glutamine in aqueous methylamine solution. Sarcosyl-L-glutamine is further treated to obtain creatyl-L-glutamine. In this way, a dipeptide creatyl-L-glutamine is obtained from glutamine.

The synthesis of creatyl-amide species of the present invention, such as for example, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine and creatyl-beta-alanyl-1-methylhistidine, can be achieved in a similar manner, except that different amino acid acids or peptides, such as L-leucine, L-carnosine, 1-methylhistidine and beta-alanyl-1-methylhistidine, are used as the starting materials. Advantageously, amide-protection of creatine carboxylic group prevents the carboxylic group and guanidine group of creatine to react and dehydrate to produce creatinine.

A further advantage of the present invention is that the amide bond of creatyl-amide species (e.g., creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine and creatyl-beta-alanyl-1-methylhistidine) can be hydrolyzed in the digestive system by enzymes to release pure creatine and useful amino acids, such as glutamine, leucine, carnosine, 1-methylhistidine and beta-alanyl-1-methylhistidine. Moreover, certain amino acids, such as leucine, have insulinogenic effects, thereby increasing insulin levels to facilitate the shuttling of amino acids into muscle.

Amide-Protected Creatine Compositions

The subject invention provides stable aqueous compositions of at least one biologically-active form of amide-protected creatine molecule. In one embodiment, the composition of the present invention comprises:

a) at least one biologically-active form of amide-protected creatine, wherein the carboxylic acid group of creatine is linked to an amino group of an amine, an amino acid or a peptide, thereby forming an amide bond; and

b) water.

In one embodiment, the amide-protected creatine is creatyl-L-glutamine or creatyl-L-leucine. In other embodiments, the amide-protected creatine molecule is creatyl-L-carnosine, creatyl-1-methylhistidine, or creatyl-beta-alanyl-1-methylhistidine. Optionally, the composition is buffered at a pH of about 1.5 to about 6.5.

The subject invention further provides methods for preparing and using these compositions.

The amide-protected creatine compositions can be formulated into nutritional supplements, aqueous and emulsion injectable formulations, aqueous clear gel systems, creams and lotions, active-in-adhesive transdermal systems, and aqueous liquid-reservoir transdermal patches.

Specifically exemplified herein are compositions for oral use. The subject invention further provides compositions for injection as well as for topical administration.

In a specific embodiment, the subject invention provides aqueous compositions suitable for oral administration to mammals including, without limitation, humans.

A composition as provided herein may be administered chronically. As used herein, "chronically" means repeated ingestion over a period of several days, several weeks, even several months, or longer. Acute (non-chronic) administration may also be utilized.

In one embodiment, the subject invention provides aqueous compositions having a pH in the range of about 1.5 to about 6.5. The pH can be obtained by using appropriate amounts of strong or weak acids or bases including, without limitation, aqueous mineral acids including HCl, H_3PO_4, and bases including sodium hydroxide, ethanolamines, etc. Preferably, the pH is from about 3.0 to about 6.5.

To prepare a composition according to one embodiment of this invention, a desired amount of creatyl-L-glutamine can be added to a selected volume of water, and sufficient stirring is affected to cause dissolution of the creatyl-L-glutamine to create an aqueous composition.

The total concentration of creatyl-L-glutamine species in an aqueous solution provided hereby may be any amount between about 0.1% and about 25% by weight based on the total weight of the aqueous solution, including all percentages and ranges of percentages therebetween.

Alternatively, creatyl-L-glutamine (or any one or more creatyl-L-glutamine species) may be added to a natural beverage in any amount provided that an aqueous solution or suspension results.

Similar embodiments of compositions may be obtained with creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine, and creatyl-beta-alanyl-1-methylhistidine.

According to additional embodiments, one or more ions selected from: sodium, potassium, zinc, calcium, and magnesium (collectively, "metal cations") are additionally present in the aqueous solution comprising creatyl-L-glutamine. These metal cations may be provided by adding a soluble salt or any other material containing any one or more of the metal cations to any aqueous solution containing creatyl-L-glutamine, or may be added to water or any aqueous solution prior to addition of one or more creatyl-L-glutamine thereto.

The total concentration of these one or more metal cations may be any amount between about 0.001% and about 10% by weight based on the total weight of the aqueous solution, including all percentages and ranges of percentages therebetween. Such metal ions may derive from a salt or compound containing a creatyl-L-glutamine, or may derive from other ingredients added to the composition. Such other ingredients include, without limitation, alkali metal halides, alkaline earth metal halides, alkali metal carboxylates, alkaline earth metal carboxylates, and any other materials known to those skilled in the nutritional arts, which comprise such metal cations as part of their molecular structure or formula, which

are not deleterious to mammalian organisms at the concentration level at which they are present, which is generally known in the art.

Similar embodiments of compositions may be obtained with creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine, and creatyl-beta-alanyl-1-methylhistidine.

A composition according to this invention may also include other ingredients such as, for example, flavoring agents, colorants, viscosity modifiers, preservatives, chelating agents, antioxidants, surface modifiers and other nutritional adjuvant materials. Other materials include any substance that is generally recognized as promoting the health or function of a mammalian organism, including humans, or benefiting a composition useful thereof in terms of its efficacy, appearance, stability, consistency, aroma, or viscosity. Such substances include, for example, other amino acids and their salts, vitamins, minerals, fatty acids, enzymes, monoglycerides, di-glycerides, tri-glyceride ester oils (including, for example, vegetable oils and animal fats) emulsifiers, hydrolyzed proteins, whey protein, stabilizers, flow modifiers, viscosity improvers, chelating agents, enzymes, and surfactants (whether anionic, cationic or nonionic). The total amount of these materials in a composition can be any amount between about 0.01% and about 50% by weight based on the total weight of said composition, including all percentages and ranges of percentages therebetween.

A composition according to this invention may also comprise one or more natural or synthetic beverages. For example, a natural beverage may contain the pulp, juice or any other constituent of a naturally-occurring fruit, vegetable, or animal product whether from the wild, cultured, cultivated on a farm or otherwise domesticated.

Natural beverages include, without limitation, materials such as milk products, soy products, ice cream, yogurt, citrus fruit juices, non-citrus fruit juices, and vegetable juices, or components of any of the foregoing, wherein said natural beverages are present in any effective amount to impart flavor to the compositions, which may be any amount between about 0.1% and about 99% by weight based on the total weight of said composition, including all percentages and ranges of percentages there between.

In general, a composition according to this invention may be provided by combining and mixing the ingredients selected, including creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine or creatyl-beta-alanyl-1-methylhistidine, and any desired quantity of any one or more other ingredients specified herein. One advantage of compositions according to this invention is that they may be packaged at pH levels as low as about pH 3, in the cold or at about room temperature or only slightly elevated temperatures, as opposed to many prior art compositions which typically require hot packaging methods that utilize specialized and expensive equipment and packaging materials.

Thus, it is evident that a composition according to this invention may be made quite palatable to a mammalian subject, including a human. Serving sizes may be any serving size in the range of about 1 milligram to about 50 grams, in an aqueous solution that is from about 20 ml to about 2500 ml in volume. The amount of creatyl-amide species (e.g. creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine and creatyl-beta-alanyl-1-methylhistidine) in an aqueous composition according to this invention is limited only by the solubility limit of the creatyl-amide species, which may exceed 50 grams per liter and concentrations at or near the solubility limit are herein provided by contacting excess amounts of the creatyl-amide species (e.g. creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine and creatyl-beta-alanyl-1-methylhistidine) with water or an aqueous solution to provide a solution saturated with creatyl-amide species (e.g. creatyl-L-glutamine, creatyl-L-leucine, creatyl-L-carnosine, creatyl-1-methylhistidine and creatyl-beta-alanyl-1-methylhistidine). Such saturated solutions can provide a concentrate from which other creatyl-amide-containing compositions may be conveniently provided.

The compositions of the subject invention can be formulated for a variety of modes of administration. These formulations include, but are not limited to, compositions for oral administration, aqueous injectable formulations, injectable emulsion compositions, gel formulations, cream formulations, transdermal systems, transdermal patch systems, liquid buccal sublingual solutions, oral solid compositions, and oral liquid composition with protein.

Physiological and Health Benefits

The compositions of the subject invention can be used in a variety of advantageous methods. For example, these compositions can be used in methods which cause regeneration of ADP to ATP in muscle tissue, cause an increase in the serum concentration of creatine, increase muscle fiber size/cross-sectional area and lean body mass, activate satellite cells, enhance memory and cognitive function, enhance the functional capacity of a mammal having a neuromuscular disease, increase muscular strength, endurance and/or power, enhance cognitive function in infants with inborn errors of creatine metabolism, or alleviate the deleterious effects of sleep deprivation.

The amide-protected creatine molecules and compositions of the subject invention offer a variety of physiological and health benefits including, for example, regeneration of ADP to ATP in the muscle tissue of the mammal, increasing serum concentration of creatine, increasing muscle fiber size/cross-sectional area and lean body mass, activating satellite cells, enhancing memory and cognitive function in the mammal, enhancing the functional capacity of a subject having a neuromuscular disease such as Huntington's disease, Parkinson's disease, or amyotrophic lateral sclerosis, increasing muscular strength, endurance and/or power, enhancing function in infants with inborn errors of creatine metabolism, and/or alleviating the deleterious effects of sleep deprivation.

In addition, creatine supplementation has beneficial effects on a subject with gyrate atrophy (a result of the inborn error of metabolism with ornithine delta-aminotransferase activity), muscular dystrophy (facioscapulohumeral dystrophy, Becker dystrophy, Duchenne dystrophy and sarcoglycan deficient limb girdle muscular dystrophy), McArdle's disease, Huntington's disease and mitochondria-related diseases. Hypoxia and energy related brain pathologies (brain trauma, cerebral ischemia, prematurity) might also benefit from creatine supplementation.

Following are examples that illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

EXAMPLE 1

Liquid Ready-to-Drink Compositions

This Example illustrates an oral liquid composition (Ready-to-Drink), comprising creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine. The composition has a pH of about 3 to 6.5, and is substantially stable at room temperature for normal warehouse storage conditions, stable

at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent or vehicle, a non-aqueous vehicle, a preservative, a physical stabilizing ingredient, one or more surfactants, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides and one or more additional components selected from lipids, starches, carbohydrates, polyols, minerals, electrolytes, amino trace elements, colorings, flavors, artificial sweeteners, and anti-oxidants.

Illustrated below is a specifically exemplified embodiment of a ready-to-drink formulation of the subject invention.

Formulation I

INGREDIENTS (Ready-to-Drink Formulation)	% w/w
Purified water	97.1
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Gamma Butyrobetaine	0.0156
Glycerin	1.067
Anserine	0.052
Caffeine	0.06
Magnesium Tanshinoate	0.0000009
L-Leucine	0.104
L-Isoleucine	0.052
L-Valine	0.0208
1,3-di-n-propyl-7-propargylxanthine	1E-10
Geranamine	0.0004
Citric acid to pH 3.33	0.179
Sodium benzoate	0.052
Potassium sorbate	0.01
Bis picolinate vanadium	0.0000002
Salt	0.005
Potassium phosphate dibasic	0.0206
Sodium Erythorbate	0.000001
Nisaplin	0.000001
Sucralose	0.073
Malic acid	0.083
Flavor Melon	0.105

EXAMPLE 2

Compositions for Buccal Sublingual Administration

This Example illustrates an oral liquid composition for buccal sublingual administration, comprising creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine. The composition has a pH of about 3 to 6.5, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent or vehicle, a non-aqueous vehicle, a preservative, a physical stabilizing ingredient, one or more surfactants, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides and one or more additional components selected from lipids, starches, carbohydrates, polyols, minerals, electrolytes, amino trace elements, colorings, flavors, artificial sweeteners, and anti-oxidants of the subject invention.

Illustrated below are specifically exemplified embodiments of liquid buccal sublingual solutions.

Formulation I

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Alcohol USP	45.0
Buffer Salt(s)	QS to adjust pH
Purified Water	QS to 100

Formulation II

INGREDIENTS	% w/w
Creatyl-L-Glutarnine or Creatyl-L-Leucine	2.10
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Ethoxydiglycol	20.0
Alcohol USP	50.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to adjust pH
Purified Water	QS to 100

Formulation III

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Propylene Glycol	20.0
Alcohol USP	40.0
Polysorbate 80	5.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to adjust pH
Purified Water	QS to 100

EXAMPLE 3

Oral Solid Compositions

This Example illustrates an oral solid composition in the form of a capsule (LICAP®) with a liquid composition as fill material containing from about 1% to about 20% of water, wherein said liquid fill material has a pH of about 3 to 6.5 and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable lipophilic solvent or vehicle, a hydrophilic non-aqueous vehicle, from about 1% to about 20% of water, a preservative, a physical stabilizing ingredient, one or more surfactants, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides and one or more additional components selected from: lipids, medium and short chain triglycerides, starches, polyols, carbohydrates, minerals, electrolytes, amino trace elements, colorings, and anti-oxidants.

Illustrated below are specifically exemplified embodiments of fill material compositions for capsule.

Formulation I

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10
Medium chain triglyceride	15.0
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.30
Oleic Acid	52.0
Purified Water	1.0-10.0

Formulation II

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.30
Polysorbate 80	25.0
PEG-40 Hydrogenated Castor Oil	38.00
PEG esters and monoglycerides	15.0
Purified Water	QS to 100

Formulation III

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.30
PEG-400	45.0
PEG esters and monoglycerides	9.00
Polysorbate 80	20.0
Buffer Salt(s)	QS to adjust pH
Purified Water	QS to 100

EXAMPLE 4

Oral Liquid Compositions

This Example illustrates an oral liquid composition containing from 1 gram to 100 grams of protein and from 1 gram to 100 g of carbohydrates per serving. The composition comprises creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises acid stable protein isolates, or a combination or blend of protein isolates, concentrates and hydrolyzates and caseins in micellar forms, a suitable aqueous solvent or vehicle, a non-aqueous vehicle, a preservative, a physical stabilizing ingredient, one or more surfactants, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides and one or more additional components selected from: lipids, starches, carbohydrates, polyols, minerals, electrolytes, amino trace elements, colorings, flavors, artificial sweeteners, and anti-oxidants.

Illustrated below are specifically exemplified embodiments of protein blend formulations.

Medium Range pH RTD Protein Blend Formulations

INGREDIENTS	% w/w	Per 16 oz Serving
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00	2.10
Whey Protein Isolate	6.000	30.00
Whey Protein Concentrate	0.640	3.20
Whey Hydrolysate	0.320	1.60
Micellar casein	0.320	1.60
Casein Protein Hydrolysate	0.000	0.00
Potassium Chloride	0.076	0.38
Ascorbic Acid	0.012	0.06
Vitamin E TPGS	0.052	0.26
Riboflavin 100	0.000	0.00000010
Niacin	0.000	0.0020
Pyrodoxine HCl	0.000	0.000007
Calcium Panthothenate	0.000	0.0011
Magnesium Maleate	0.020	0.1000
d-ribose	0.040	0.2000
Centromix E	0.600	3.00
Saflower Oil	1.200	6.00
Sunflower Oil	1.200	6.00
Medium Chain Triglycerides	0.800	4.00
L-Glutamine	0.025	0.13
Glucose Polymers (Rice trin)	0.800	4.00
Waxy Maize Starch	1.000	5.00
High Amylose Starch (Amylose ADP11P)	0.100	0.50
Magnesium Citrate	0.124	0.62
Microcrystalline Cellulose	0.100	0.50
Malic Acid	0.140	0.70
Citric acid to pH 6.5	0.566	2.83
Sodium Citrate to pH 6.5	0.140	0.70
Sucralose	0.011	0.06
Glycerin	3.000	15.00
Na 2 EDTA	0.050	0.25
Sodium Benzoate	0.090	0.45
Potassium Sorbate	0.190	0.95
Water	QS	QS

Low pH RTD Protein Formulations

INGREDIENTS	Per 16 oz serving	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10	0.25
Whey Protein Isolate Acid Stable	44.44	9.26
Sucralose	0.12	0.025

-continued

Low pH RTD Protein Formulations

INGREDIENTS	Per 16 oz serving	% w/w
Na EDTA	0.24	0.050
Potassium Sorbate	0.96	0.200
Sodium Benzoate	0.48	0.100
Citric Acid to pH 3.0	QS	QS
Malic Acid to pH 3.0	QS	QS
Water	433.8	90.37
	480	100
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10	0.25
Whey Protein Isolate Acid Stable	44.44	9.26
Sucralose	0.12	0.025
Waxy Maize Starch	4.80	1.00
Glucose Polymers (Rice trin)	0.96	0.20
Na EDTA	0.24	0.050
Potassium Sorbate	0.96	0.200
Sodium Benzoate	0.48	0.100
Citric Acid to pH 3.0	QS	QS
Malic Acid to pH 3.0	QS	QS
Water	QS	QS
TOTAL	480	100

EXAMPLE 5

Aqueous Injectable Compositions

This Example illustrates an aqueous injectable composition suitable for human administration, wherein said composition is isotonic and sterile in nature. The composition comprises creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, and wherein said injectable preparation has a pH of about 3, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent, a preservative, a physical stabilizing ingredient and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, peptides, proteins and carbohydrates.

Illustrated below are specifically exemplified embodiments of aqueous injectable formulations.

Formulation I

INGREDIENTS	% w/v
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
AMP	12.5
UTP	0.10
Amino Acids	3.0-7.0
Polysorbate 80	0.40
Sodium CMC	0.50
Sodium Chloride	0.90
Benzyl alcohol	0.90
Buffer Salt(s)	QS to adjust to pH 3-6.5
Sodium Hydroxide	QS to adjust to pH 3-6.5
Water for Injection	QS to 100

Formulation II

INGREDIENTS	% w/v
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
AMP	12.50
UTP	0.10
Amino Acids	3.0-7.0
Polysorbate 80	0.40
Sorbitol	40.00
Sodium Chloride	0.90
Benzyl alcohol	0.90
Buffer Sat(s)	QS to adjust to pH 3-6.5
Sodium Hydroxide	QS to adjust to pH 3-6.5
Water for Injection	QS to 100

Formulation III

INGREDIENTS	% w/v
Creatyl-L-Glutamine or Creatyl-L-Leucine	2.10
Polysorbate 80	0.40
AMP	12.50
UTP	0.10
Amino Acids	3.0-7.0
Sodium Citrate	0.50
Sodium Chloride	0.90
Benzyl alcohol	0.90
Buffer Salt(s)	QS to adjust to pH 3-6.5
Sodium Hydroxide	QS to adjust to pH 3-6.5
Water for Injection	QS to 100

EXAMPLE 6

Emulsion Injectable Compositions

This Example illustrates an emulsion injectable composition suitable for human administration, wherein said composition is isotonic and sterile in nature. The composition comprises creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, and wherein said injectable preparation has a pH of about 3, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent, pharmaceutically acceptable oil (sesame, olive, castor, peanut, cotton seed, etc.), a natural emulsifier such as lecithin or any other synthetic emulsifier being of the polysorbate or ethoxylated glyceride type, a preservative, a physical stabilizing ingredient and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, peptides, proteins and carbohydrates.

Illustrated below are specifically exemplified embodiments of emulsion injectable formulations.

Formulation I

INGREDIENTS	% w/v
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
AMP	12.5
UTP	0.10
Amino Acids	3.0-7.0
Sesame Oil	2.0-12.0
Polysorbate 80	0.40
Sodium Chloride	0.90
Benzyl alcohol	0.90
Buffer Salt(s)	QS to adjust to pH 3-6.5
Sodium Hydroxide	QS to adjust to pH 3-6.5
Water for Injection	QS to 100

Formulation II

INGREDIENTS	% w/v
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
AMP	12.50
UTP	0.10
Amino Acids	3.0-7.0
Olive Oil	1.0-15.0
Lecithin	0.50-5.0
Sorbitol	30.00
Sodium Chloride	0.90
Benzyl alcohol	0.90
Buffer Sat(s)	QS to adjust to pH 3-6.5
Sodium Hydroxide	QS to adjust to pH 3-6.5
Water for Injection	QS to 100

Formulation III

INGREDIENTS	% w/v
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Peanut Oil	1.0-15.0
Polysorbate 80	0.2-10.0
AMP	12.50
UTP	0.10
Amino Acids	3.0-7.0
Sodium Citrate	0.50
Sodium Chloride	0.90
Benzyl alcohol	0.90
Buffer Salt(s)	QS to adjust to pH 3-6.5
Sodium Hydroxide	QS to adjust to pH 3-6.5
Water for Injection	QS to 100

EXAMPLE 7

Gel Topical Compositions for Skin Application

This Example illustrates a gel topical composition for skin application in humans and animals, wherein said composition is clear or slightly opaque and has a gel consistency so that it can be spread on skin surface. The composition comprises creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, has a pH of about 3 to 6.5, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent, a preservative, a polymer for imparting consistency, a physical stabilizing ingredient and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides, proteins and carbohydrates.

Illustrated below are specifically exemplified embodiments of gel formulations.

Formulation I

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Peptides/Polypeptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Propylene Glycol	12.0
Carbomer	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Methylparaben	0.20
Propylparaben	0.10
Purified Water	QS to 100

Formulation II

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Peptides/Polypepetides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Glycerin	5.00
Hydroxyethylcellulose	2.00
Triethanolamine	QS to pH 3.0-6.5
Methylparaben	0.20
Propylparaben	0.10
Purified Water	QS to 100

Formulation III

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Peptides/Polypepetides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Glycerin	15.0
Poloxamers 407/188	10.00
Triethanolamine	QS to pH 3.0-6.5
Methylparaben	0.025
Propylparaben	0.015
Purified Water	QS to 100

EXAMPLE 8

Cream Topical Compositions for Skin Application

This Example illustrates a cream topical composition for skin application in humans and animals, wherein said com-

position is an emulsion system or an opacified gel system, and has a creamy consistency so that it can be spread on skin surface. The composition comprises creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, has a pH of about 3 to 6.5, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent, a preservative, a physical stabilizing ingredient, a surfactant, moisturizers, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides, proteins and carbohydrates.

Illustrated below are specifically exemplified embodiments of cream formulations.

Formulation I

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
White Petrolatum	20.0
Stearyl Alcohol	20.0
Propylene Glycol	12.0
Peptides/Polypeptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Sodium lauryl sulfate	1.00
Methylparaben	0.20
Propylparaben	0.10
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

Formulation II

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Peptides/Polypeptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Mineral Oil	15.0
Lanolin Alcohol	10.0
Cetyl Alcohol	0.20
Beeswax	4.00
Sorbitan Monoleate	5.00
Glycerin	5.00
Borax	0.30
Triethanolamine	0.70
Methylparaben	0.20
Propylparaben	0.10
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

Formulation III

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	1.00
Peptides/Polypeptides	3.00

-continued

Formulation III

INGREDIENTS	% w/w
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Glyceryl Monostearate	10.0
Lanolin	2.00
Glycerin	10.0
Stearyl Pyridinium Chloride	1.50
Methylparaben	0.025
Propylparaben	0.015
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

EXAMPLE 9

Deep-Penetrating Transdermal Compositions

This Example illustrates a deep-penetrating transdermal composition for application in humans and animals, wherein said composition is a solution, a gel-like or an emulsion-like system or an opacified gel-like system, and has a consistency so that it can be spread on skin surface. The composition comprises creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, and is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent, a non-aqueous solvent, one or more penetrating enhancers, a preservative, a physical stabilizing ingredient, one or more surfactants, moisturizers, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides, proteins and carbohydrates.

Illustrated below are specifically exemplified embodiments of transdermal compositions.

Formulation I

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	5.00
N-methylpyrrolidone	15.0
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Alcohol USP	2.00
Benzyl alcohol	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

Formulation II

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	5.00
Peptides	3.00

-continued

Formulation II

INGREDIENTS	% w/w
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Ethoxydiglycol	25.0
Alcohol USP	2.00
PEG esters and monoglycerides	15.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

Formulation III

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	5.00
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Propylene Glycol	25.0
Alcohol USP	4.00
Polysorbate 80	10.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

EXAMPLE 10

Transdermal Patch Delivery Systems

This Example illustrates a transdermal patch delivery system, comprising a liner, an adhesive, a backing and an aqueous liquid reservoir composition. The aqueous liquid reservoir composition is a solution or a suspension, comprising creatyl-amide species, such as creatyl-L-glutamine or creatyl-L-leucine, wherein said transdermal patch is substantially stable at room temperature for normal warehouse storage conditions, stable at 104° F. (40° C.) for shipping in hot weather trucks and/or overseas containers, and stable at 39° F. (4° C.) in coolers so that it can be stored under refrigeration conditions.

Preferably, the composition comprises a suitable aqueous solvent, a non-aqueous solvent, one or more penetrating enhancers, a preservative, a physical stabilizing ingredient, one or more surfactants, and/or one or more buffer salts that can render the composition pH stable. The composition may also contain nucleotides, oligonucleotides, the monophosphates, diphosphates, triphosphates and cyclic derivatives of these nucleotides, amino acids, vitamins and vitamin-like isoprenoids, peptides, proteins and carbohydrates.

Illustrated below are specifically exemplified embodiments of liquid reservoirs for transdermal patch.

Formulation I

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	5.00
N-methylpyrrolidone	10.0
Peptides	3.00
AMP	12.50

-continued

Formulation I

INGREDIENTS	% w/w
UTP	0.10
Ubiquinone	3.20
Alcohol USP	45.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

Formulation II

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	5.00
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Ethoxydiglycol	20.0
Alcohol USP	50.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

Formulation III

INGREDIENTS	% w/w
Creatyl-L-Glutamine or Creatyl-L-Leucine	5.00
Peptides	3.00
AMP	12.50
UTP	0.10
Ubiquinone	3.20
Propylene Glycol	20.0
Alcohol USP	40.0
Polysorbate 80	5.0
Benzyl alcohol	1.00
Buffer Salt(s)	QS to pH 3.0-6.5
Purified Water	QS to 100

EXAMPLE 11

Stability of Creatyl-Amide Compositions

This Example demonstrates that amide protected bioactive creatine compositions of the subject invention are stable at room temperature, refrigeration temperature and elevated temperature. Specifically exemplified herein are three different formulations prepared using stable creatyl-L-glutamine (C-L-G) at a concentration of 1.00 mg/ml between pH 3.0 to 7.0. These formulations are described below.

Formulation I

INGREDIENTS Formulation pH 3.33	% w/w
Purified water	97.1
Creatyl-L-Glutamine	1
Gamma Butyrobetaine	0.0156
Glycerin	1.067
Anserine	0.052
Caffeine	0.06

-continued

Formulation I

INGREDIENTS Formulation pH 3.33	% w/w
Magnesium Tanshinoate	0.0000009
L-Leucine	0.104
L-Isoleucine	0.052
L-Valine	0.0208
1,3-di-n-propyl-7-propargylxanthine	1E-10
Geranamine	0.0004
Citric acid to pH 3.33	0.179
Sodium benzoate	0.052
Potassium sorbate	0.01
Bis picolinate vanadium	0.0000002
Salt	0.005
Potassium phosphate dibasic	0.0206
Sodium Erythorbate	0.000001
Nisaplin	0.000001
Sucralose	0.073
Malic acid	0.083
Flavor Melon	0.105

Formulation II

INGREDIENTS Formulation pH 7-8	% w/w
Purified water	99.0
Creatyl-L-Glutamine	1.0

Formulation III

INGREDIENTS Formulation pH 3.33	% w/w
Purified water	97.1
Creatyl-L-Glutamine	1
Citric acid to pH 3.33	0.179
Sodium benzoate	0.052
Potassium sorbate	0.01
Potassium phosphate dibasic	0.0206
Sucralose	0.073
Malic acid	0.083
Flavor Melon	0.105

The above described formulations were stored in glass vials at room temperature (25° C., 77° F.), at refrigerator temperature (4° C., 39° F.) and at elevated temperature (40° C., 104° F.) in vials. These samples were assayed by HPLC at periodic intervals for minimum of 60 days for creatyl-L-glutamine (C-L-G) and creatinine (degradation product of creatine) content. The % recovery results are presented below.

Ready To Drink Formulation (pH = 3.3)

	Room Temperature		4° C. (39° F.)		40° C. (104° F.)	
	C-L-G	Creatinine	C-L-G	Creatinine	C-L-G	Creatinine
Initial	98.81	1.19	N/A	N/A	N/A	N/A
1 Day	99.16	0.84	99.23	0.77	98.92	1.08
3 Days	98.76	1.24	98.96	1.04	97.96	2.04
1 Week	98.91	1.09	99.28	0.72	97.05	2.95
2 Weeks	98.59	1.41	99.27	0.73	95.45	4.55
3 Weeks	98.33	1.67	99.16	0.84	94.49	5.51
4 Weeks	97.95	2.05	98.98	1.02	93.25	6.75

-continued

Ready To Drink Formulation (pH = 3.3)

	Room Temperature		4° C. (39° F.)		40° C. (104° F.)	
	C-L-G	Creatinine	C-L-G	Creatinine	C-L-G	Creatinine
6 Weeks	97.41	2.59	98.22	1.78	89.12	10.88
2 Months	97.45	2.55	98.88	1.12	87.46	11.50
3 Months	94.32	5.68	94.67	5.33	89.83	10.17

Neutral Formulation (pH = 7.0-8.0)

	Room Temperature		4° C. (39° F.)		40° C. (104° F.)	
	C-L-G	Creatinine	C-L-G	Creatinine	C-L-G	Creatinine
Initial	99.15	0.85	N/A	N/A	N/A	N/A
1 Day	99.15	0.85	99.20	0.80	98.77	1.23
3 Days	98.41	1.59	99.11	0.89	89.95	10.05
1 Week	93.53	6.47	99.09	0.91	91.03	8.97
2 Weeks	74.62	25.38	99.03	0.97	27.12	72.88
3 Weeks	52.89	47.11	98.95	1.05	36.96	63.04
4 Weeks	39.47	60.53	99.00	1.00	16.15	83.85
6 Weeks	5.47	94.53	97.29	2.71	0.00	100.00
2 Months	0.00	100.00	97.90	2.10	0.00	100.00
3 Months	0.00	100.00	97.77	2.23	0.00	100.0

Acidic Formulation (pH = 3.3)

	Room Temperature		4° C. (39° F.)		40° C. (104° F.)	
	C-L-G	Creatinine	C-L-G	Creatinine	C-L-G	Creatinine
Initial	99.23	0.77	N/A	N/A	N/A	N/A
1 Day	99.17	0.83	99.23	0.77	98.89	1.11
3 Days	99.03	0.97	93.52	0.74	98.21	1.79
1 Week	98.91	1.09	99.30	0.70	97.31	2.69
2 Weeks	98.91	1.09	99.29	0.71	95.87	3.62
3 Weeks	98.47	1.53	99.19	0.81	94.94	5.06
4 Weeks	98.12	1.88	98.97	1.03	93.71	6.29
6 Weeks	96.42	3.58	98.32	1.68	89.69	10.31
2 Months	96.76	3.24	98.50	1.50	89.05	10.95
3 Months	95.63	4.37	96.365	3.65	88.90	11.10

The results show that creatyl-L-glutamine (C-L-G) aqueous solutions of the subject invention remain stable for more than 90 days at room temperature (25° C., 77° F.) and refrigerator temperature (4° C., 39° F.), and thus are suitable for normal warehouse storage conditions and also refrigeration conditions. The C-L-G composition is also stable for more than 30 days at elevated temperature (40° C., 104° F.), which is suitable for shipping in hot weather trucks and/or overseas containers.

EXAMPLE 12

Conversion of Creatine to Creatinine

The following tables illustrate the rate of conversion to creatinine from creatine monohydrate and disodium creatine phosphate tetrahydrate solutions.

Preparation: Creatine Monohydrate Aqueous Solution
Concentration: 0.250 mg/mL
pH: 7.0 Condition: 40 C.°

Test	Time: INITIAL	3 day	31 Days
COP Assay	0.257 mg/mL	0.242 mg/ml	0.251 mg/mL
Creatinine	0.000 mg/mL	0.008 mg/mL	0.068 mg/mL
pH	7.0		

Preparation: Creatine Monohydrate Aqueous Solution
Concentration: 0.250 mg/mL

Test	Time: INITIAL	3 day	10 days	21 days	39 Days
pH: 3.0 Condition: 40 C.°					
COP Assay	0.245 mg/mL	0.091 mg/ml	0.036 mg/mL	0.029 mg/mL	0.030 mg/mL
Creatinine	0.000 mg/mL	0.125 mg/mL	0.177 mg/ml	0.186 mg/mL	0.186 mg/mL
pH	3.0				
pH: 3.0 Condition: 25 C.°					
COP Assay	0.245 mg/mL	0.219 mg/ml	0.214 mg/mL	0.151 mg/mL	0.072 mg/mL
Creatinine	0.000 mg/mL	0.026 mg/mL	0.072 mg/ml	0.111 mg/mL	0.154 mg/mL
pH	3.0				

Preparation: Disodium Creatine Phosphate Tetrahydrate Aqueous Solution
Concentration: 0.250 mg/mL

Test	Time: INITIAL	3 day	10 days	21 days	39 Days
pH: 7.0 Condition: 40 C.°					
COP Assay	0.247 mg/mL	0.166 mg/ml	0.066 mg/mL	0.015 mg/mL	0.002 mg/mL
Creatine Monohydrate	0.00 mg/mL	0.042 mg/mL	0.114 mg/mL	0.122 mg/mL	0.108 mg/mL
Creatinine	0.000 mg/mL	0.004 mg/mL	0.012 mg/mL	0.020 mg/ml	0.030 mg/mL
pH	7.0				
pH: 7.0 Condition: 25 C.°					
COP Assay	0.247 mg/mL	0.229 mg/ml	0.231 mg/mL	0.182 mg/mL	0.141 mg/mL
Creatine Monohydrate	0.00 mg/mL	0.0.14 mg/mL	0.041 mg/mL	0.069 mg/mL	0.089 mg/mL
Creatinine	0.000 mg/mL	0.000 mg/mL	0.000 mg/mL	0.000 mg/ml	0.000 mg/mL
pH	7.0				

1. Preparation: Disodium Creatine Phosphate Tetrahydrate Aqueous Solution
Concentration: 0.250 mg/mL

Test	Time: INITIAL	3 day	10 days	21 days	39 Days
pH: 3.0 Condition: 40 C.°					
COP Assay	0.247 mg/mL	0.000 mg/ml	0.000 mg/mL	0.000 mg/mL	0.000 mg/ml
Creatine Monohydrate	0.004 mg/mL	0.042 mg/mL	0.017 mg/mL	0.011 mg/mL	0.012 mg/ml
Creatinine	0.000 mg/mL	0.054 mg/mL	0.086 mg/mL	0.080 mg/ml	0.081 mg/mL

-continued

1. Preparation: Disodium Creatine Phosphate Tetrahydrate Aqueous Solution Concentration: 0.250 mg/mL

	Time				
Test	INITIAL	3 day	10 days	21 days	39 Days
pH	3.0				
	pH: 3.0 Condition: 25 C.				
COP Assay	0.247 mg/mL	0.000 mg/ml	0.000 mg/mL	0.000 mg/mL	0.00 mg/ml
Creatine Monohydrate	0.000 mg/ml	0.095 mg/mL	0.092 mg/mL	0.065 mg/mL	0.031 mg/mL
Creatinine	0.000 mg/mL	0.014 mg/mL	0.034 mg/mL	0.050 mg/ml	0.069 mg/mL
pH	3.0				

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What is claimed is:

1. An aqueous composition for administering, to a mammal, an amide-protected, biologically active form of creatine that is stable in an aqueous system, wherein said composition comprises:

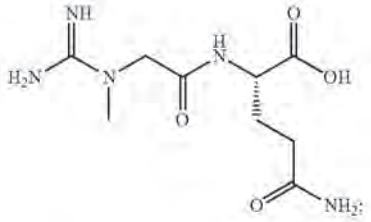
a) at least one creatyl-amide species, and

b) water;

wherein, in said creatyl-amide species, the carboxylic acid group of creatine is linked, via an amide bond, to an amino group of a species selected from the group consisting of glutamine, leucine, arginine, histidine, isoleucine, lysine, methionine, threonine, tryptophan, tyrosine, valine, alanine, asparagine, aspartate, cysteine, glutamate, glycine, proline, serine, carnosine, 1-methylhistidine, beta-alanyl-1-methylhistidine sarcosine, β-alanine, citrulline, ornithine, prolinamide, 5-hydroxylysine, alanyl-L-glutamine, taurine, and geranamine.

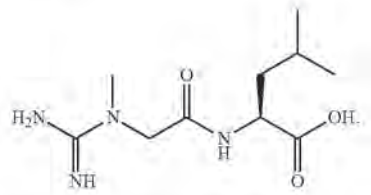
2. The composition, according to claim **1**, wherein the creatyl-amide species is:

creatyl-L-glutamine



or

creatyl-L-leucine



3. The composition, according to claim **1**, wherein the creatyl-amide species is: creatyl-L-carnosine, creatyl-1-methylhistidine, or creatyl-beta-alanyl-1-methylhistidine.

4. The composition, according to claim **1**, having a pH of about 1.5 to about 6.5.

5. The composition, according to claim **1**, wherein said at least one creatyl-amide species is present in an amount between about 0.01% and about 10% by weight.

6. The composition, according to claim 1, further comprising one or more ions selected from the group consisting of: sodium, potassium, zinc, calcium, and magnesium.

7. The composition, according to claim 6, wherein said one or more ions is present in an amount between about 0.001% and about 5% by weight.

8. The composition, according to claim 1, further comprising one or more additional materials selected from the group consisting of flavoring agents, colorants, viscosity modifiers, preservatives, fragrances, amino acids and their salts, vitamins, minerals, fatty acids, enzymes, co-enzymes, monoglycerides, di-glycerides, tri-glyceride ester oils emulsifiers, hydrolyzed proteins, whey protein, stabilizers, flow modifiers, chelating agents, anti-oxidants, anti-microbials, benzoates, alcohols, esters of para-hydroxybenzoic acid, propionates, and surfactants.

9. The composition, according to claim 1, further comprising one or more beverages selected from the group consisting of milk products, soy products, ice cream, yogurt, citrus fruit juices, non-citrus fruit juices, and vegetable juices.

10. The composition, according to claim 1, comprising an anti-microbial preservative present in an effective amount to inhibit microbial growth, wherein the preservative is selected from the group consisting of an ester of para-hydroxy benzoic acid, an ester of propionates, and a sorbate salt.

11. The composition, according to claim 1, in the form of a composition for oral administration, an aqueous injectable formulation, an injectable emulsion composition, a gel formulation, a cream formulation, a transdermal system, a transdermal patch system, a liquid buccal sublingual solution, an oral solid composition, or an oral liquid composition with protein.

12. The composition, according to claim 1, which is a liquid composition.

* * * * *

EXHIBIT 17

FREQUENTLY ASKED QUESTIONS

F YOUR BRAND AMBASSADOR/ BANG ENERGY MODEL?

OLICY?

AMPLES?

S IN BANG® / REDLINE®?

IN VPX SRO™ WHEY PROTEIN ISOLATE?

NE FOUND IN BANG® RTD AND BANG MASTER BLASTER®

found in BANG® RTD and Bang Master Blaster®?

are, creatine is not stable in liquids. VPX Sports® have created novel a creatine compounds that allow creatine to maintain i
s patent-pending novel water stable covalently bonded creatine/leucine peptide. BANG ® is the **only carbonated beverage** tha
o deliver creatine along with other health nutrients into the body.

TER I TAKE NO SHOTGUN MY BLOOD SUGAR DROPS.

SITY STUDIES ON VPX PRODUCTS? WHERE DO I GET INFO ON STUDIES ON THE VPX PRODUCT LINE?

TGUN® OR BANG MASTER BLASTER®?

EXHIBIT 18

Beverage daily.com

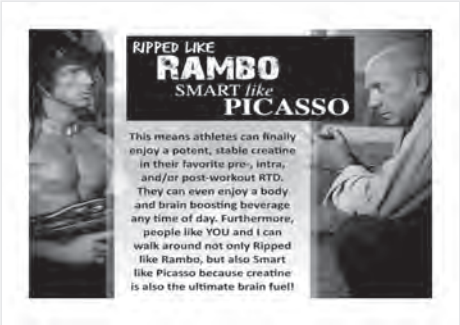
SPORTS NUTRITION 2014: FOCUS ON CREATINE SCIENCE

‘Get ripped like Rambo and smart like Picasso!’ VPX rips up sports drink rulebook

By Ben BOUCKLEY

10-Sep-2014 - Last updated on 12-Sep-2014 at 13:08 GMT

RELATED TAGS: Muscle



VPX/Redline CEO Jack Owoc tells Sports Nutrition 2014 delegates how to create a creatine-based sports/energy drink that’s 'omnipresent enough to crush Red Bull, Powerade and Monster'.

Speaking at yesterday’s online event in a webinar called ‘Sports Drink Divorce: A Two-Tier Market Emerges’ – you can watch his presentation here* – Owoc dismissed *“old school energy drinks…with sugar, artificial colors, BVO and who knows what else”.*

Showing a slide with a cooler full of Vitamin Water on a ’10 for $10’ promotion Owoc slammed the mainstream US market and called for a new means of formulating and marketing beverages.

“Look at these sugar drinks! No-one’s making money, no-one’s having fun, performance isn’t being increased, muscle mass isn’t being enhanced.”

Owoc said VPX/Redline brands Bang and Shotgun 5X fuse three multi-billion dollar categories: Creatine ($6bn), sports drinks ($7.5bn) and energy drinks ($9.4bn in America alone).

'A $15.5bn market? That's chump change!'

“If you could create a hybridized sports drink with an energy component and creatine, you could tap into a $22.9bn market,” he said, dismissing a Mintel August 2014 prediction of the best case growth scenario for sports drinks – growing from a $9.43bn market today into a $15.514bn market by 2019 – as *“chump change”*, if one could hit

Owoc said the patented drink is first to market and is a *"huge success in the marketplace already"* – a claim that Nielsen data for the year ending January 18 2014 bears out.

This shows 1,758% y-o-y growth for VPX Bang (then a $465,000+ brand) and Owoc said it had grown exponentially since then; larger VPX brands including Redline ($37.5m sales), VPX Redline Xtreme ($28.2m), VPX Redline Power Rush ($5.7m) and VPX Redline Original ($3.49m) also feature.

VPX Sports' Bang energy drink is growing fast in the US, as Neilsen data show

"We occupy four spaces in the Nielsen report on nutritional supplements. We're not a one-hit wonder like some of our competitors. We're not just talking – what I'm saying is, it's real," Owoc said.

Early adoption in US gyms nationwide

VPX's portfolio sold in places that Red Bull and Gatorade don't even sell, Owoc added, citing GNCs and hardcore gyms across America as early adopters.

Despite people associating creatine with steroid use Owoc insisted this couldn't be further from the truth, claiming that 1,300+ studies proved its safety and efficacy.

Creatine increases energy levels, strength and the ability to exercise harder and longer, he said, noting that VPX holds patents for water stable 'super creatine' peptides.

Owoc said creatine also offered brain performance benefits, and that 'cognitive creatine' even had potential to treat Alzheimer's, Parkinson's and other forms of dementia.

Future creatine research will look at brain not brawn

"Creatine can make you ripped like Rambo and smart like Picasso. In the future, mark my words, all the research on creatine will be about the brain rather than brawn," Owoc said.

Asking rhetorically how brands could create a drink, *"omnipresent enough to crush Red Bull, Monster and Powerade all at the same time"*, Owoc said they had to play a different game.

"When everyone is zigging, you gotta zag! You gotta be that purple cow in that field of lame brown cows!"

*Register for free to view our online webinars, and tell us what you think! #SportsNutrition14

RELATED TOPICS: Ingredients, Energy & Sports, Natural and Organic, Functional Beverages

EXHIBIT 19

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bangenergy.ceo ⭐⭐⭐NEW BANG STUDY PROVES BANG IS BAD ASS!⭐⭐⭐
💪 BANG Enhances Mental Focus!
💪 Bang Enhances Reaction Time! 💪
Bang Improves Psychomotor Vigilance

Bang is the ULTIMATE BRAIN & BODY FUEL! .
HUGE announcement Please watch to the end OF VIDEO!

.

👉 It is believed that regular caffeine use will lose its effectiveness with continue use over time.

.

Researchers examined daily caffeine intake and divided test subjects into

17,035 views

MARCH 15

Add a comment...

081

EXHIBIT 20


083
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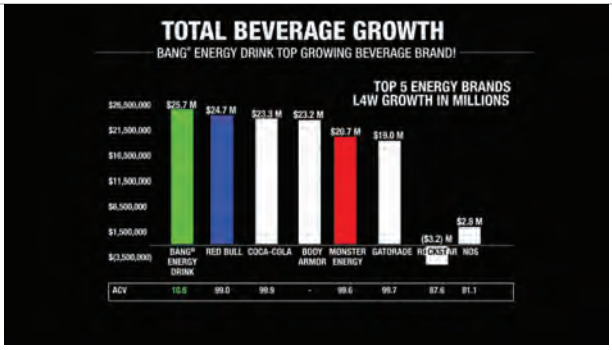
EXHIBIT 21

NEWS PROVIDED BY
Bang Energy →
Sep 26, 2018, 12:11 ET

WESTON, Fla., Sept. 26, 2018 /PRNewswire/ -- On September 4, 2018, Monster Energy filed a federal lawsuit against VPX and its CEO, CSO, and Bang® Energy founder, Jack Owoc. This is the second lawsuit Monster has filed against VPX.

So, what is the real reason why competitors are so worried about Bang? If you have any doubts, the chart below will clear up any confusion. Bang is not only America's top growing energy drink. By beating multi-billion-dollar giants, Bang is the #1 overall growth-beverage in the entire non-alcoholic beverage industry! And, Bang's monumental achievement was accomplished with just 10.6% market share compared with other famous beverages having market share 8 to 10 times greater than Bang. A meritless and frivolous lawsuit has no chance to prevent the inevitability of Bang's meteoric rise to the top!



So, what is the real reason why competitors are so worried about Bang? If you have any doubts, the chart above will clear up any confusion. Bang is not only America's top growing energy drink. By beating multi-billion-dollar giants, Bang is the #1 overall growth-beverage in the entire non-alcoholic beverage industry! And, Bang's monumental achievement was accomplished with just 10.6% market share compared with other famous beverages having market share 8 to 10 times greater than Bang. A meritless and frivolous lawsuit has no chance to prevent the inevitability of Bang's meteoric rise to the top!

Despite Mr. Owoc's innovations being backed by 27 of the most revolutionary beverage and supplement studies in the history of sports nutrition and filing seven significant patents including what may be the greatest beverage and sports nutrition patent ever filed – the water stable Super Creatine® patent –all contribute in part to Bang's rise to prominence.

Bang Energy's Chief Scientific Officer and CEO, Jack Owoc, who has seven issued U.S. patents responds, "Consumers choose Bang® because it's more effective, tastes better, and doesn't contain harmful amounts of sugar and ingredients like D-glucuronolactone contained in Monster." Unfortunately, little research has been done on D-glucuronolactone in humans. (Ref. 4) Two studies have been done on Monster, and neither have proven that Monster can improve exercise performance (Ref. 1,2).

Is a Sugary Caffeinated Drink an Energy Drink or does it Rob your Body of Energy?

VPX / Bang's science is the best in the business. Bang's marketing message is fresh, exciting and crystal clear.

Caffeinated energy drinks with massive amounts of sugar can cause a sugar-induced crash. When a ginormous 50+ gram amount of liquid sugar enters the blood, the body responds to this metabolic crisis by over-expressing insulin. Insulin overload then drives blood sugar dangerously low causing the bewildered consumer to crash and energy levels to rapidly decrease. Therefore, there exists a critical biological and legal argument here – if a so called "energy drink" causes you to crash and in doing so zaps your energy, can these beverages be legally marketed as energy drinks? Are these high sugar metabolic-dysregulating drinks really "energy drinks"?

(5). Furthermore, research has shown that a single 24 ounce high sugar, carbonated energy drink can have adverse health effects (5). This research has also shown that caffeine at doses of 300 mg or less is safe alone but when combined with sugar it can be dangerous (6). Therefore, consumers are increasingly looking for superior, sugar-free alternatives like Bang®."

--Jack Owoc

Bang Finishes First!

For our customers and retailers who have supported us and our products, we appreciate your loyalty and only hope that we can help you in accomplishing your fitness and health goals! Bang® Master Blaster has also been found to be safe in a university study. VPX has sold over 100,000,000 cans of Bang®, and to best of its knowledge, not one adverse event has been reported.

"Bang® and all products created by the world's leading innovator in research proven performance enhancing beverages and sports nutrition, Jack Owoc, always places safety and efficacy first." Jack stated, "We would never make the gross scientific mistake of combining 54 grams of sugar with caffeine. Everything we do is highly researched and science-driven. We are the most prolific innovator of university research-backed products in the history of sports nutrition. In fact, I believe we have conducted more university studies than most of the sports nutrition industry combined!"

"With 9 years of teaching, 6 different science disciplines, 7 issued U.S. patents, and 27 university studies under my belt, it's shocking that a competitive energy drink company would question my unrivaled scientific acumen." – Jack Owoc

and defend against Monster's baseless lawsuit. For more information about Bang®, contact: Marc J. Kesten at Legal@vpxsports.com

Scientific References

1. Michael T Nelson, et al. Cardiovascular and ride time-to-exhaustion effects of an energy drink. Journal of the International Society of Sports Nutrition 201411:2

2. Gabriel J Sanders, et al. The effect of three different energy drinks on oxygen consumption and perceived exertion during treadmill exercise. Journal of the International Society of Sports Nutrition

3. Fletcher EA, Lacey et al. Randomized Controlled Trial of High-Volume Energy Drink Versus Caffeine Consumption on ECG and Hemodynamic Parameters. J Am Heart Assoc. 2017 Apr 26;6(5):

4. Higgins JP, et al. Energy Beverages: Content and Safety. Mayo Clinic Proceedings. 2010;85(11):1033-1041. doi:10.4065/mcp.2010.0381.

5. Higgins JP et al. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. World Journal of Cardiology. 2017;9(2):162-166. doi:10.4330/wjc.v9.i2.162.

6. Heckman, M. A., et al. (2010), Caffeine (1, 3, 7-trimethylxanthine) in Foods: A Comprehensive Review on Consumption, Functionality, Safety, and Regulatory Matters. Journal of Food Science, 75: R77–R87.

7. Bio-available N-acetyl creatine species and compositions thereof: https://patents.google.com/patent/US9642825

EXHIBIT 22

bangenergy.ceo • Follow

jahshlott What's the benefit of drinking bang over Monster zero or other sugar free energy drinks? I'm a huge Bang fan (and VPX fan in general) and i push your product in my area as much as possible. There are just haters out there because of the myth of what energy drinks will do. They need to know =}

72w 2 likes Reply

Hide replies

robsures @jahshlott thats a great question that we've been asked in our shop.

1,260 views

NOVEMBER 15, 2017

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091

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robsures @jahshlott thats a great question that we've been asked in our shop.

72w 2 likes Reply

bangenergy.ceo @jahshlott Super Creatine which is a patented creatine-amino acid peptide that's stable and water. BCAAs, CoQ10 and @bangenergy Comes in 18 mind blowing flavors!

72w 3 likes Reply

1,260 views

NOVEMBER 15, 2017

Add a comment...

092

EXHIBIT 23

European Food Safety Authority

EFSA Journal 2011;9(7):2303

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to creatine and increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924), increase in endurance capacity (ID 1527, 1535), and increase in endurance performance (ID 1521, 1963) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to creatine and increase in physical performance during short-term, high intensity, repeated exercise bouts, increase in endurance capacity, and increase in endurance performance. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The food constituent that is the subject of the health claims is creatine. The Panel considers that creatine is sufficiently characterised.

Increase in physical performance during short-term, high intensity, repeated exercise bouts

The claimed effects are “energy metabolism”, “muscular effort”, “bodily constitution”, “increasing strength”, “increasing mass”, “increasing power”, “increasing performance”, “muscular

[1] On request from the European Commission, Question No EFSA-Q-2008-1526, EFSA-Q-2008-2257, EFSA-Q-2008-2258, EFSA-Q-2008-2259, EFSA-Q-2008-2260, EFSA-Q-2008-2262, EFSA-Q-2008-2263, EFSA-Q-2008-2264, EFSA-Q-2008-2268, EFSA-Q-2008-2269, EFSA-Q-2008-2270, EFSA-Q-2008-2271, EFSA-Q-2008-2272, EFSA-Q-2008-2655, EFSA-Q-2008-2656, EFSA-Q-2008-2657, EFSA-Q-2008-2696, adopted on 30 June 2011.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank for the preparatory work on this scientific opinion: The members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen. The members of the Claims Sub-Working Group on Weight Management/Satiety/Glucose and Insulin Control/Physical Performance: Kees de Graaf, Joanne Harrold, Mette Hansen, Mette Kristensen, Anders Sjödin and Inge Tetens.

Suggested citation: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to creatine and increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924), increase in endurance capacity (ID 1527, 1535), and increase in endurance performance (ID 1521, 1963) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(7):2303. [24 pp.]. doi:10.2903/j.efsa.2011.2303. Available online: www.efsa.europa.eu/efsajournal

effort/recovery", "increasing time to exhaustion" and "increasing lifting volume and performance". The target population is assumed to be adults performing high-intensity exercise. In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effects refer to an increase in physical performance during short-term, high intensity, repeated exercise bouts. The Panel considers that an increase in physical performance during short-term, high intensity, repeated exercise bouts is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that there is good consensus on the role of creatine in increasing physical performance during short-term, high intensity, repeated exercise bouts, and that the meta-analyses and individual intervention studies provided in the consolidated list are consistent with this consensus.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of creatine and an increase in physical performance during short-term, high intensity, repeated exercise bouts.

The Panel considers that in order to obtain the claimed effect, 3 g of creatine should be consumed daily. The target population is adults performing high-intensity exercise.

Increase in endurance capacity

The claimed effect is "increasing workout capacity". The target population is assumed to be adults performing endurance exercise. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to an increase in endurance capacity. The Panel considers that an increase in endurance capacity is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that the three human intervention studies provided from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of creatine supplementation on measures of endurance capacity.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of creatine and an increase in endurance capacity.

Increase in endurance performance

The claimed effects are "muscular effort" and "creatine: energy reserve of muscle tissue". The target population is assumed to be adults performing endurance exercise. In the context of the proposed wordings, the Panel assumes that the claimed effects refer to increase in endurance performance (i.e. during longer-term exercise generally at intensity <80 % of maximum O_2 consumption). The Panel considers that an increase in endurance performance is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that one meta-analysis of 18 human intervention studies, and one additional study, did not show an effect of creatine supplementation on measures of endurance performance.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of creatine and an increase in endurance performance.

KEY WORDS

Creatine, physical performance, endurance capacity, endurance performance, exercise, health claims.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

EFSA DISCLAIMER

See Appendix B

INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006[4] submitted by Member States contains main entry claims with corresponding conditions of use and literature for similar health claims. EFSA has screened all health claims contained in the original consolidated list of Article 13 health claims which was received by EFSA in 2008 using six criteria established by the NDA Panel to identify claims for which EFSA considered sufficient information had been provided for evaluation and those for which more information or clarification was needed before evaluation could be carried out[5]. The clarifications which were received by EFSA through the screening process have been included in the consolidated list. This additional information will serve as clarification to the originally provided information. The information provided in the consolidated list for the health claims which are the subject of this opinion is tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claims is creatine.

Creatine is a non-essential nitrogenous organic acid that occurs in vertebrates, and it is also synthesised in the human body from L-arginine, glycine and L-methionine. Approximately 95 % of the creatine pool in the body is located in skeletal muscle. The content of creatine in foods can be measured by established methods.

The Panel considers that the food constituent, creatine, which is the subject of the health claims, is sufficiently characterised.

2. Relevance of the claimed effect to human health

2.1. Increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924)

The claimed effects are “energy metabolism”, “muscular effort”, “bodily constitution”, “increasing strength”, “increasing mass”, “increasing power”, “increasing performance”, “muscular effort/recovery”, “increasing time to exhaustion”, and “increasing lifting volume and performance”. The Panel assumes that the target population is adults performing high-intensity exercise.

In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effects refer to an increase in physical performance during short-term, high intensity, repeated exercise bouts. Physical performance relates to the ability to complete certain tasks with higher intensity, faster, or with a higher power output. Muscle mass and strength are major determinants of physical performance. In repeated exercise bouts, physical performance is also related to the ability of muscle to recover faster from high-intensity exercise.

The Panel considers that an increase in physical performance during short-term, high intensity, repeated exercise bouts is a beneficial physiological effect.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

[5] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

2.2. Increase in endurance capacity (ID 1527, 1535)

The claimed effect is "increasing workout capacity". The Panel assumes that the target population is adults performing endurance exercise.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to an increase in endurance capacity. Endurance capacity refers to the exercise time to self-reported fatigue when exercising at a constant workload or speed.

The Panel considers that an increase in endurance capacity is a beneficial physiological effect.

2.3. Increase in endurance performance (ID 1521, 1963)

The claimed effects are "muscular effort" and "creatine: energy reserve of muscle tissue". The Panel assumes that the target population is adults performing endurance exercise.

In the context of the proposed wordings, the Panel assumes that the claimed effects refer to an increase in endurance performance (i.e. during longer-term exercise generally at intensity <80 % of maximum O_2 consumption). Endurance performance relates to the ability to complete certain tasks with higher intensity, faster, or with a higher power output when performing long-term exercise.

The Panel considers that an increase in endurance performance is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The references provided in the consolidated list in relation to the claims evaluated in this opinion included narrative reviews and book chapters which contained no original data for the scientific substantiation of the claims, and abstracts and conference proceedings reporting on human intervention studies in which the information provided regarding the study design, methodology and statistical analyses was insufficient for a full scientific evaluation. Some of the references reported on human intervention studies in which creatine was administered in combination with other food constituents (e.g. carbohydrates, protein, micronutrients and fatty acids) so that the study design did not allow conclusions to be drawn on the effect of creatine alone. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claims.

The references provided also included statements/consensus opinions from authoritative bodies such as the Agence Française de Sécurité Sanitaire des Aliments (AFSSA, 2000), the Scientific Committee on Food (SCF, 2001), and the American College of Sports Medicine (Terjung et al., 2000). Other consensus opinions were published by the International Society of Sports Nutrition (Buford et al., 2007; Kreider et al., 2010) and the American Dietetic Association (Rodriguez et al., 2009). Two meta-analyses of human intervention studies (Branch, 2003; Nissen and Sharp, 2003) and one "systematic review" (Rawson and Volek, 2003) which addressed the effects of creatine consumption on outcome measures relevant to the claimed effects evaluated in this opinion, considered the vast majority of individual human intervention studies submitted for the scientific substantiation of the claims. In addition, three of the references provided which reported on human intervention studies and which addressed the effects of creatine on outcome measures related to the claimed effects evaluated in this opinion were not included in the meta-analyses described below, and will be considered separately as appropriate (Izquierdo et al., 2002; Ostojic, 2004; Syrotuik et al., 2001).

The purpose of the "systematic review" by Rawson and Volek (2003) was to address the effects of creatine supplementation and concurrent resistance training on muscle strength and weight lifting performance. A total of 22 studies, 14 of which were already included in the meta-analysis by Nissen and Sharp (2003), met the inclusion criteria of Rawson and Volek (2003) and the remaining, except three (Stevenson and Dudley, 2001; Syrotuik et al., 2000; Syrotuik et al., 2001), were considered in

the meta-analysis by Branch (2003). Two of the three references were provided in the consolidated list as individual studies (Stevenson and Dudley, 2001; Syrotuik et al., 2001). The Panel notes that the methodology (e.g. literature search or other strategies used to identify pertinent references, and methodology used to calculate average percent estimates for increases in muscle strength and weight lifting performance) used in this review is poorly described and that all the studies included were already considered in the meta-analyses provided or were submitted separately. The Panel considers that no conclusions can be drawn from this review for the scientific substantiation of the claims evaluated in this opinion.

The meta-analysis by Branch (2003) included 96 publications (published up to December 2000) from 100 randomised, placebo-controlled trials, in which at least subjects were blinded to the intervention. These studies comprised 1,847 subjects. Results were given as means±SEM and 95 % CI. Mean sample size was 19±1 (range 4 to 80). Most of the studies (93 %) were published after 1994, and most (71 % of the studies) were randomised, double-blind, placebo-controlled interventions which addressed the effect of an acute (≤14 days) creatine loading regimen (19.7±0.5 g creatine for an average of 9±1 days) on physical performance in mostly young trained (77 % of the studies) men (68 % of the studies). Only 22 studies investigated the effects of low dose maintenance creatine supplementation (>14 days) following acute creatine loading. Twenty-four studies included men and women as subjects. The effect of creatine supplementation on women was the focus in only 9 studies. The primary objective of the meta-analysis was to quantify the effect of creatine supplementation on body composition (including lean body mass) and exercise performance. Performance tasks were classified as single-bout or repetitive-bout exercises. The first bout of repetitive-bout exercises was classified as a single-bout exercise task. Performance tasks of ≤30 sec, 30 to 150 sec, and >150 sec were also analysed separately. The effect size (ES) of creatine supplementation variable was calculated for each dependent.

The meta-analysis by Nissen and Sharp (2003) assessed the effects of longer-term creatine supplementation on lean body mass and muscle strength during resistance training. Only randomised, placebo-controlled human intervention studies, published in peer reviewed journals between 1967 and 2001, of at least 3 weeks duration and which involved a full-body resistance-training regimen two or more times per week and were conducted in healthy adults who were not under dietary restriction were included. A total of 18 studies using creatine alone as intervention met the inclusion criteria. These studies included a total of 368 subjects (n=180 in the intervention group and n=188 in the control group) with a mean age of 24 years. All studies had a parallel design, and the sample size in individual studies was generally small (mean n=10 per group). All studies included were published between 1997 and 2001. Three studies included men and women, three studies included women only, and the remaining studies were conducted in men only. Five studies were conducted in untrained subjects, and 13 studies in trained individuals. The studies averaged 7.5 weeks (range 3-13 weeks) in duration. The average loading dose of creatine was 19.4 g/day (range 10-21 g/day) for 5.3 days (range 4-7 days), and the average maintenance dose was 6.7 g/day (range 2-10.5 g/day). Changes in lean mass and strength were normalised for inclusion in the meta-analysis by conversion to percentage change per week for both treatment and placebo groups. Effect sizes (ES) of lean mass and strength changes were calculated for each dependent variable. Duration of tasks and task repetition were not considered in the analysis. All the studies included in this meta-analysis except four (Arciero et al., 2001; Bemben et al., 2001; Chrusch et al., 2001; Jowko et al., 2001) were already considered in the meta-analysis by Branch (2003).

These references will be referred to in different sections of the present evaluation as appropriate.

3.1. Increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924)

The evidence provided by consensus opinions/reports from authoritative bodies and reviews shows that there is good consensus on the role of creatine in increasing physical performance during short-term, high intensity, repeated exercise bouts (AFSSA, 2000; Buford et al., 2007; Kreider et al., 2010; Rodriguez et al., 2009; SCF, 2001; Terjung et al., 2000).

Creatine phosphate (CrP) serves as a readily available source of energy in skeletal muscle and other tissues. For most exercise situations, the demand for adenosine triphosphate (ATP) is predominantly provided through oxidative phosphorylation in the mitochondria. However, when aerobic energy production cannot meet the demand for ATP, anaerobic energy production from CrP hydrolysis and glycogenolysis/glycolysis is required to assist in the provision of ATP. Such cases include the transition from rest to exercise, the transition from one power output to a higher power output, and power outputs above 90-100 % maximal oxygen consumption (VO_2max). The rapid re-phosphorylation of adenosine diphosphate (ADP) from CrP via the creatine kinase reaction may buffer changes in ATP during transitions between rest and exercise, and may contribute a substantial fraction of ATP synthesis during short duration, high intensity exercise (AFSSA, 2000; Buford et al., 2007; SCF, 2001; Terjung et al., 2000).

During a bout of high intensity exercise, the relative importance of CrP hydrolysis to ATP synthesis falls off as the exercise duration is increased beyond a few seconds. The greatest improvements in performance following short-term creatine supplementation (5-7 days of ~20 g/day) are found during a series of repetitive, high power output exercise bouts. Exercise performance during the latter bouts of a series (e.g. third, fourth and fifth) can be increased by 5-20 % in very high power output exercise bouts that can be maintained for only a short (seconds) period (e.g. maximal cycling and/or power jumping), and are separated by fairly brief periods of rest (e.g. 20-60 seconds). Therefore, it is likely that creatine supplementation improves exercise performance in sport events which require explosive, high-energy output activities, especially of a repeated nature (AFSSA, 2000; Buford et al., 2007; SCF, 2001; Terjung et al., 2000).

Creatine ingestion increases the total creatine content in human muscle by approximately 15-20 % (mean value), albeit a high inter-individual variability exists. Such increases can be achieved by ingestion of 20 g per day for 4-5 days, but also by ingestion of 3 g per day over a period of one month. The increased creatine content in human muscle is maintained when the ingestion is reduced to 2 g per day after the original loading period. There is a substantial reduction in urine production on the first three days of the loading period and this reduction is coincident with the retention of creatine. The retention of water is thought to be related to an osmotic load caused by creatine retention and to account for the rapid-onset weight gain experienced by many individuals ingesting creatine. Many studies have reported increases in body mass of 1-3 kg following short-term (5-7 days) creatine supplementation (AFSSA, 2000; Buford et al., 2007; SCF, 2001; Terjung et al., 2000).

Longer-term creatine supplementation (e.g. 4 to 12 weeks) in combination with training appears to increase muscle mass and strength as a result of an improved ability to perform high-intensity exercise via increased CrP availability (Buford et al., 2007; SCF, 2001).

The meta-analyses and individual intervention studies provided in the consolidated list are consistent with the above-mentioned consensus. In the meta-analysis by Branch (2003), anaerobic exercise performance capacity during high-intensity, short-duration exercise (≤30 sec) was significantly increased by creatine supplementation (617 performance variables; ES=0.24±0.002, 95 % CI=0.20, 0.28; $p<0.05$), and the majority of the studies considered (45 out of 61) reported an ergonomic effect of creatine. Significantly more repetitions at specific submaximal intensity/workload (21 estimates; ES=0.64±0.18, 95 % CI=0.27, 1.00, $p<0.05$) and greater work capacity (83 estimates; ES=0.21±0.05,

95 % CI=0.11, 0.30, n=83, p<0.05) were performed during consumption of creatine compared to placebo. ES for repetitive-bout exercise was significantly higher than for single-bout exercise, and mean ES for percentage decrement in performance over multiple high-intensity bouts was not significantly different from zero (ES= –0.04±0.06; 95 %CI= –0.16, 0.09), suggesting a resistance to fatigue between exercise bouts associated with creatine supplementation. The effect of creatine on overall exercise performance was still significant, but less evident, for tasks lasting 30 to 150 sec (135 performance estimates; ES=0.19±0.05, 95 % CI=0.10, 0.28; p<0.05), and it was non-significant for tasks lasting more than 150 sec (ES=0.09±0.07; 95 % CI= –0.04, 0.22). On the other hand, the meta-analysis by Nissen and Sharp (2003) supports a positive effect of longer-term (3-13 weeks) creatine supplementation on lean body mass (ES=0.26; 95 % CI=0.17, 0.34, p<0.001) and strength (ES=0.36; CI=0.28, 0.43, p<0.001) during repetitive resistance training, possibly owing to an improved ability to perform high-intensity exercise.

In weighing the evidence, the Panel took into account that there is good consensus on the role of creatine in increasing physical performance during short-term, high intensity, repeated exercise bouts, and that the meta-analyses and individual intervention studies provided in the consolidated list are consistent with this consensus.

The Panel concludes that a cause and effect relationship has been established between the consumption of creatine and an increase in physical performance during short-term, high intensity, repeated exercise bouts.

3.2. Increase in endurance capacity (ID 1527, 1535)

Among the references provided in the consolidated list, three reported on individual human intervention studies which investigated the effect of creatine supplementation on continuous (Zoeller et al., 2007) or intermittent (Izquierdo et al., 2002; Ostojic, 2004) endurance cycling or running capacity. Two of the studies tested the effects of an acute creatine load (Izquierdo et al., 2002; Ostojic, 2004), whereas one study used an acute creatine load followed by a creatine maintenance phase (Zoeller et al., 2007).

Izquierdo et al. (2002) investigated the effects of acute creatine supplementation (20 g/day for five days) on endurance capacity in trained male handball players randomly assigned to either creatine (n=9) or placebo (maltodextrin; n=10). Before and after supplementation, subjects performed a maximal multistage discontinuous incremental running test to exhaustion. No significant differences in endurance capacity were observed between the creatine and placebo groups. Ostojic et al. (2004) examined the effects of a seven-day creatine supplementation (30 g/day) *vs*. placebo (cellulose) on endurance capacity assessed by a maximal multistage 20 m shuttle run test in 20 young soccer players in a randomised parallel study. No significant differences between the creatine and placebo groups were observed. In the study by Zoeller et al. (2007), 55 men (24.5±5.3 years) were randomly assigned to one of the following supplementation groups for four weeks: placebo (34 g glucose/day, n=13), creatine (5.25 g/day creatine monohydrate plus 34 g glucose, n=12), beta-alanine (n=14), or beta-alanine plus creatine (n=16). Prior to and following supplementation, participants performed a graded exercise test on a cycle ergometer to determine time to exhaustion. The initial power output was set at 30 watts and increased 30 watts every two minutes until the subject could not maintain the required power output at a pedaling rate of 70 rpm, or until volitional termination owing to fatigue. No significant differences in time to exhaustion were observed between groups.

The Panel notes that the three human intervention studies provided did not show an effect of creatine supplementation on measures of endurance capacity. The Panel also notes that there is no consensus on the role of creatine in increasing endurance (aerobic) capacity (AFSSA, 2000; Buford et al., 2007; Kreider et al., 2010; SCF, 2001; Terjung et al., 2000).

In weighing the evidence, the Panel took into account that the three human intervention studies provided from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of creatine supplementation on measures of endurance capacity.

The Panel concludes that a cause and effect relationship has not been established between the consumption of creatine and an increase in endurance capacity.

3.3. Increase in endurance performance (ID 1521, 1963)

In the meta-analysis by Branch (2003), half of the studies (nine studies out of 18) which investigated the effect of creatine supplementation on measures of performance during continuous, long-term aerobic exercise (>150 sec) in endurance sports (running and swimming) did not show an effect of creatine supplementation compared to placebo, and the overall effect was not significant (ES=0.09±0.07; 95 % CI= –0.04, 0.22) after exclusion of an outlier with a large ES.

Among the references provided in the consolidated list, one reported on an individual human intervention study which investigated the effect of creatine supplementation on measures of endurance performance (Syrotuik et al., 2001), and was not included in the meta-analysis by Branch (2003).

Syrotuik et al. (2001) randomised 22 rowers to consume either creatine (0.3 g/kg/day for five days followed by a five-week maintenance dose of 0.03 g/kg/day) or placebo together with training (continuous and interval rowing and resistance training 4 and 2 days per week, respectively) for six weeks. No significant differences in repeated power interval performance or 2,000 m rowing times were observed compared to placebo during the five-day creatine loading or the five-week maintenance phases. The Panel notes that this study does not show an effect of creatine supplementation on endurance performance.

The Panel notes that one meta-analysis of 18 human intervention studies, and one additional study, did not show an effect of creatine supplementation on measures of endurance performance. The Panel also notes that there is no consensus on the role of creatine in increasing endurance (aerobic) performance (AFSSA, 2000; Buford et al., 2007; Kreider et al., 2010; SCF, 2001; Terjung et al., 2000).

In weighing the evidence, the Panel took into account that one meta-analysis of 18 human intervention studies, and one additional study, did not show an effect of creatine supplementation on measures of endurance performance.

The Panel concludes that a cause and effect relationship has not been established between the consumption of creatine and an increase in endurance performance.

4. Panel's comments on the proposed wording

4.1. Increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924)

The Panel considers that the following wording reflects the scientific evidence: "Consumption of creatine increases physical performance during short-term, high intensity, repeated exercise bouts".

5. Conditions and possible restrictions of use

5.1. Increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924)

The Panel considers that in order to obtain the claimed effect, 3 g of creatine should be consumed daily. The target population is adults performing high-intensity exercise.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, creatine, which is the subject of the health claims, is sufficiently characterised.

Increase in physical performance during short-term, high intensity, repeated exercise bouts (ID 739, 1520, 1521, 1522, 1523, 1525, 1526, 1531, 1532, 1533, 1534, 1922, 1923, 1924)

- The claimed effects are “energy metabolism”, “muscular effort”, “bodily constitution”, “increasing strength”, “increasing mass”, “increasing power”, “increasing performance”, “muscular effort/recovery”, “increasing time to exhaustion” and “increasing lifting volume and performance”. The target population is assumed to be adults performing high-intensity exercise. In the context of the proposed wordings and the references provided, it is assumed that the claimed effects refer to an increase in physical performance during short-term, high intensity, repeated exercise bouts. An increase in physical performance during short-term, high intensity, repeated exercise bouts is a beneficial physiological effect.
- A cause and effect relationship has been established between the consumption of creatine and an increase in physical performance during short-term, high intensity, repeated exercise bouts.
- The following wording reflects the scientific evidence: “Consumption of creatine increases physical performance during short-term, high intensity, repeated exercise bouts”.
- In order to obtain the claimed effect, 3 g of creatine should be consumed daily. The target population is adults performing high-intensity exercise.

Increase in endurance capacity (ID 1527, 1535)

- The claimed effect is “increasing workout capacity”. The target population is assumed to be adults performing endurance exercise. In the context of the proposed wordings, it is assumed that the claimed effect refers to an increase in endurance capacity. An increase in endurance capacity is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of creatine and an increase in endurance capacity.

Increase in endurance performance (ID 1521, 1963)

- The claimed effects are “muscular effort” and “creatine: energy reserve of muscle tissue”. The target population is assumed to be adults performing endurance exercise. In the context of the proposed wordings, it is assumed that the claimed effects refer to increase in endurance performance. An increase in endurance performance is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of creatine and an increase in endurance performance.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1526, EFSA-Q-2008-2257, EFSA-Q-2008-2258, EFSA-Q-2008-2259, EFSA-Q-2008-2260, EFSA-Q-2008-2262, EFSA-Q-2008-2263, EFSA-Q-2008-2264, EFSA-Q-2008-2268, EFSA-Q-2008-2269, EFSA-Q-2008-2270, EFSA-Q-2008-2271, EFSA-Q-2008-2272, EFSA-Q-2008-2655, EFSA-Q-2008-2656, EFSA-Q-2008-2657, EFSA-Q-2008-2696). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: http://www.efsa.europa.eu/panels/nda/claims/article13.htm.

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APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[6] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[7]

Foods are commonly involved in many different functions[8] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[6] OJ L12, 18/01/2007
[7] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[8] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.

- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.

- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.
- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

APPENDIX C

Table 1. Main entry health claims related to creatine, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
739	Creatine	Energy metabolism	Support in case of intense physical activity/contributes to increased muscle strength/contributes to increased muscle torque production/contributes to increased training intensity workouts/contributes to increased work capacity/contributes to increased muscle fatigue resistance/helps reduce muscle fatigue during exercise/supplementation increases muscle creatine and phospho creatine levels/supplementation increases muscle energy stores/contributes to increased lean body weight.
	Conditions of use - Max 3 g per day.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1520	Creatine	Energy metabolism	Support in case of intense physical activity -contributes to increased muscle strength -contributes to increased muscle torque production -contributes to increased training intensity workouts -contributes to increased work capacity
	Conditions of use - A minimum of 6-20g daily - A minimum of 7.7g per day - Max 3 g per day - Initialdosis: bis 20 g/Tag, während 7 Tagen–Erhaltungsdosis: 2-4 g/Tag - Sportlernahrung–Startphase: 4 Wo. 3g/d, Erhaltungsphase: 2-3g/d - Sportler–Gemeinsam mit viel Flüssigkeit–Tagesdosis Kreatinmonohydrat: 1500 mg - 0,5 g pro Tag		

ID	Food or Food constituent	Health Relationship	Proposed wording
1521	Creatine	Muscular effort	Strengthens /supports /assists human energy reserves Supports the building of muscle Supports the building of muscle improves physical performance
	Conditions of use - Initial phase: 4 Weeks 3g/day, Sustainment: 2-3g/day A minimum of 7.7g per day for claims relating to exercise performance and a minimum of 6g daily for claims relating to body composition		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1522	Creatine	Muscular effort / Recovery	Diminish fatigue after rapid physical activity / For quicker recovery after rapid physical exertion
	Conditions of use - Initial phase: 4 Weeks 3g/day, Sustainment: 2-3g/day A minimum of 7.7g per day for claims relating to exercise performance		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1523	Creatine	Bodily Constitution	supports the creating of lean tissue mass (fat free muscle)
	Conditions of use - Initial phase: 4 Weeks 3g/day, Sustainment: 2-3g/day. A minimum of 6g daily for claims relating to body composition		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1525	Creatine	Increasing Strength	Creatine has been shown to increase strength. Creatine has the ability to enhance muscular strength Ingredient clinically shown to help boost strength Boost muscular strength
	Conditions of use - The product must contain at least 1 gram creatine per serving Claim to be used for foods for active individuals. A minimum of 7.7g per day for claims relating to improvements in strength - Drink with creatine content of 0.05-0.1g/100g, 0.13-0.25g/serving, 0.25-0.5g/daily serving.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1526	Creatine	Increasing Mass	Creatine has been shown to increase lean muscle mass Creatine has the ability to enhance muscle growth With proper diet and exercise, creatine can help support an increase in fat free mass. Ingredient clinically shown to help boost lean body mass

	Conditions of use - The product must contain at least 1 gram creatine per serving Claim to be used for foods for active individuals. A minimum of 6g per day for claims relating to improvements in lean muscle mass		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1527	Creatine	Increasing Workout Capacity	Creatine can help enhance physical working capacity at fatigue threshold
	Conditions of use - The product must contain at least 1 gram creatine per serving. Claim to be used for foods for active individuals. A minimum of 6g per day for claims relating to increasing workout capacity		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1531	EAS Creatine (EAS Phosphagen)	Increasing Strength	Gains in Lean Muscle Mass EAS Creatine (EAS Phosphagen) is clinically shown effective for building muscle mass" NOT "EAS Creatine (formally Phosphagen)
	Conditions of use - The product must contain at least 5 gram creatine monohydrate per serving Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1532	EAS Creatine (EAS Phosphagen)	Increasing Mass	EAS Creatine (EAS Phosphagen) is clinically shown to help: Support Gains in Lean Muscle Mass EAS Creatine (formerly Phosphagen) is clinically shown effective for building muscle mass
	Conditions of use - The product must contain at least 5 gram creatine monohydrate per serving. Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1533	EAS Creatine (EAS Phosphagen)	Increasing Lifting Volume and Performance	EAS Creatine (EAS Phosphagen) is clinically shown to help increase lifting volume.
	Conditions of use - The product must contain at least 5 gram creatine monohydrate per serving. Claim to be used for foods for active individuals		

ID	Food or Food constituent	Health Relationship	Proposed wording
1534	EAS Creatine (EAS Phosphagen)	Increasing Power	EAS Creatine (EAS Phosphagen) is clinically shown to help: Increase Power EAS Creatine (EAS Phosphagen) is clinically shown effective for improving muscular power
	Conditions of use - The product must contain at least 5 gram creatine monohydrate per serving. Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1535	EAS Creatine (EAS Phosphagen)	Increasing Work Capacity	EAS Creatine (EAS Phosphagen) is clinically tested to improve anaerobic work capacity
	Conditions of use - The product must contain at least 5 gram creatine per serving. Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1922	Creatine	Increasing Performance	Creatine can help support an increase in peak muscular performance.
	Conditions of use - The product must contain at least 1 gram creatine per serving. Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1923	Creatine	Increasing Power	Creatine can help support a muscular environment to enhance explosive movements. Ingredient clinically shown to help boost power. Boost muscular power
	Conditions of use - Claim to be only used for dietetic foods/food supplements for sportpeople under the Dir. 89/398/EEC - 3 g/day - The product must contain at least 1 gram creatine per serving		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1924	EAS Creatine (EAS Phosphagen)	Increasing time to exhaustion	EAS Creatine (EAS Phosphagen) is clinically shown to increase total time to exhaustion in intense repeated exercise bouts
	Conditions of use - The product must contain at least 5 gram creatine monohydrate per serving - Claim to be used for foods for active individuals		

ID	Food or Food constituent	Health Relationship	Proposed wording
1963	Sportfoods Clarification provided Creatine, condition of use: 3g / day (for dietetic foods/food supplements for sportpeople)	Creatine : energy reserve of muscle tissue	Increases muscle power and speed', 'Provide energy to muscle'
	Conditions of use - Claim to be only used for dietetic foods/food supplements for sportpeople under the Dir. 89/398/EEC - 3 g/day		

GLOSSARY AND ABBREVIATIONS

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
CI	Confidence interval
CrP	Creatine phosphate
ES	Effect size
Rpm	Revolution per minute
SEM	Standard error of the mean
VO_2max	Maximal oxygen consumption

EXHIBIT 24

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International Society of Sports Nutrition position stand: creatine supplementation and exercise

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A Position Statement and Review of the Literature

Position Statement: The following nine points related to the use of creatine as a nutritional supplement constitute the Position Statement of the Society. They have been approved by the Research Committee of the Society.

1. Creatine monohydrate is the most effective ergogenic nutritional supplement currently available to athletes in terms of increasing high-intensity exercise capacity and lean body mass during training.

2. Creatine monohydrate supplementation is not only safe, but possibly beneficial in regard to preventing injury and/or management of select medical conditions when taken within recommended guidelines.

3. There is no scientific evidence that the short- or long-term use of creatine monohydrate has any detrimental effects on otherwise healthy individuals.

4. If proper precautions and supervision are provided, supplementation in young athletes is acceptable and may provide a nutritional alternative to potentially dangerous anabolic drugs.

5. At present, creatine monohydrate is the most extensively studied and clinically effective form of creatine for use in nutritional supplements in terms of muscle uptake and ability to increase high-intensity exercise capacity.

6. The addition of carbohydrate or carbohydrate and protein to a creatine supplement appears to

increase muscular retention of creatine, although the effect on performance measures may not be greater than using creatine monohydrate alone.

7. The quickest method of increasing muscle creatine stores appears to be to consume ~0.3 grams/kg/day of creatine monohydrate for at least 3 days followed by 3–5 g/d thereafter to maintain elevated stores. Ingesting smaller amounts of creatine monohydrate (e.g., 2–3 g/d) will increase muscle creatine stores over a 3–4 week period, however, the performance effects of this method of supplementation are less supported.

8. Creatine products are readily available as a dietary supplement and are regulated by the *U.S. Food and Drug Administration (FDA)*. Specifically, in 1994, U.S. President Bill Clinton signed into law the Dietary Supplement Health and Education Act (DSHEA). DSHEA allows manufacturers/companies /brands to make structure-function claims; however, the law strictly prohibits disease claims for dietary supplements.

9. Creatine monohydrate has been reported to have a number of potentially beneficial uses in several clinical populations, and further research is warranted in these areas.

The following literature review has been prepared by the authors in support of the aforementioned position statement.

Creatine Supplementation and Exercise: A Review of the Literature

Introduction

The use of creatine as a sport supplement has been surrounded by both controversy and fallacy since it gained widespread popularity in the early 1990's. Anecdotal and media reports have often claimed that creatine usage is a dangerous and unnecessary practice; often linking creatine use to anabolic steroid abuse [1]. Many athletes and experts in the field have reported that creatine supplementation is not only beneficial for athletic performance and various medical conditions but is also clinically safe [2-5]. Although creatine has recently been accepted as a safe and useful ergogenic aid, several myths have been purported about creatine supplementation which include:

1. All weight gained during supplementation is due to water retention.

2. Creatine supplementation causes renal distress.

3. Creatine supplementation causes cramping, dehydration, and/or altered electrolyte status.

4. Long-term effects of creatine supplementation are completely unknown.

5. Newer creatine formulations are more beneficial than creatine monohydrate (CM) and cause fewer side effects.

6. It's unethical and/or illegal to use creatine supplements.

While these myths have been refuted through scientific investigation, the general public is still primarily exposed to the mass media which may or may not have accurate information. Due to this confounding information, combined with the fact that creatine has become one of the most popular nutritional supplements on the market, it is important to examine the primary literature on supplemental creatine ingestion in humans. The purpose of this review is to determine the present state of knowledge concerning creatine supplementation, so that reasonable guidelines may be established and unfounded fears diminished in regard to its use.

Background

Creatine has become one of the most extensively studied and scientifically validated nutritional ergogenic aids for athletes. Additionally, creatine has been evaluated as a potential therapeutic agent in a variety of medical conditions such as Alzheimer's and Parkinson's diseases. Biochemically speaking, the energy supplied to rephosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) during and following intense exercise is largely dependent on the amount of phosphocreatine (PCr) stored in the muscle [6,7]. As PCr stores become depleted during intense exercise, energy availability diminishes due to the inability to resynthesize ATP at the rate required to sustained high-intensity exercise [6,7]. Consequently, the ability to maintain maximal-effort exercise declines. The availability of PCr in the muscle may significantly influence the amount of energy generated during brief periods of high-intensity exercise. Furthermore, it has been hypothesized that increasing muscle creatine content, via creatine supplementation, may increase the availability of PCr allowing for an accelerated rate of resynthesis of ATP during and following high-intensity, short-duration exercise [6-12]. Theoretically, creatine supplementation during training may lead to greater training adaptations due to an enhanced quality and volume of work performed. In terms of potential medical applications, creatine is intimately involved in a number of metabolic pathways. For this reason, medical researchers have been investigating the potential therapeutic role of creatine supplementation in a variety of patient populations.

Creatine is chemically known as a non-protein nitrogen; a compound which contains nitrogen but is not a protein per se [13]. It is synthesized in the liver and pancreas from the amino acids arginine, glycine, and methionine [9,13,14]. Approximately 95% of the body's creatine is stored in skeletal muscle. Additionally, small amounts of creatine are also found in the brain and testes [8,15]. About two thirds of the creatine found in skeletal muscle is stored as phosphocreatine (PCr) while the remaining amount of creatine is stored as free creatine [8]. The total creatine pool (PCr + free creatine) in skeletal muscle averages about 120 grams for a 70 kg individual. However, the average human has the capacity to store up to 160 grams of creatine under certain conditions [7,9]. The body breaks down about 1 – 2% of the creatine pool per day (about 1–2 grams/day) into creatinine in the skeletal muscle [13]. The creatinine is then excreted in urine [13,16]. Creatine stores can be replenished by obtaining creatine in the diet or through endogenous synthesis of creatine from glycine, arginine, and methionine [17,18]. Dietary sources of creatine include meats and fish. Large amounts of fish and meat must be consumed in order to obtain gram quantities of creatine. Whereas dietary supplementation of creatine provides an inexpensive and efficient means of increasing dietary availability of creatine without excessive fat and/or protein intake.

Supplementation Protocols and Effects on Muscle Creatine Stores

Various supplementation protocols have been suggested to be efficacious in increasing muscle stores of creatine. The amount of increase in muscle storage depends on the levels of creatine in the muscle prior to supplementation. Those who have lower muscle creatine stores, such as those who eat little meat or fish, are more likely to experience muscle storage increases of 20–40%, whereas those with relatively high muscle stores may only increase stores by 10–20% [19]. The magnitude of the increase in skeletal muscle creatine content is important because studies have reported performance changes to be correlated to this increase [20,21].

The supplementation protocol most often described in the literature is referred to as the "loading" protocol. This protocol is characterized by ingesting approximately 0.3 grams/kg/day of CM for 5 – 7 days (e.g., ≃5 grams taken four times per day) and 3–5 grams/day thereafter [18,22]. Research has shown a 10–40% increase in muscle creatine and PCr stores using this protocol [10,22]. Additional research has reported that the loading protocol may only need to be 2–3 days in length to be beneficial, particularly if the ingestion coincides with protein and/or carbohydrate [23,24]. Furthermore,

supplementing with 0.25 grams/kg-fat free mass/day of CM may be an alternative dosage sufficient to increase muscle creatine stores [25].

Other suggested supplementation protocols utilized include those with no loading phase as well as "cycling" strategies. A few studies have reported protocols with no loading period to be sufficient for increasing muscle creatine (3 g/d for 28 days) [15] as well as muscle size and strength (6 g/d for 12 weeks) [26,27]. These protocols seems to be equally effective in increasing muscular stores of creatine, but the increase is more gradual and thus the ergogenic effect does not occur as quickly. Cycling protocols involve the consumption of "loading" doses for 3–5 days every 3 to 4 weeks [18,22]. These cycling protocols appear to be effective in increasing and maintaining muscle creatine content before a drop to baseline values, which occurs at about 4–6 weeks [28,29].

Creatine Formulations and Combinations

Many forms of creatine exist in the marketplace, and these choices can be very confusing for the consumer. Some of these formulations and combinations include creatine phosphate, creatine + β-hydroxy-β-methlybutyrate (HMB), creatine + sodium bicarbonate, creatine magnesium-chelate, creatine + glycerol, creatine + glutamine, creatine + β-alanine, creatine ethyl ester, creatine with cinnulin extract, as well as "effervescent" and "serum formulations". Most of these forms of creatine have been reported to be no better than traditional CM in terms of increasing strength or performance [30-38]. Reliable studies are yet to be published for creatine ethyl ester and creatine with cinnulin extract. Recent studies do suggest, however, that adding β-alanine to CM may produce greater effects than CM alone. These investigations indicate that the combination may have greater effects on strength, lean mass, and body fat percentage; in addition to delaying neuromuscular fatigue [31,32].

Three alternative creatine formulations have shown promise, but at present do not have sufficient evidence to warrant recommendation in lieu of CM. For example, creatine phosphate has been reported to be as effective as CM at improving LBM and strength, [36] yet this has only been reported in one study. In addition, creatine phosphate is currently more difficult and expensive to produce than CM. Combining CM with sodium phosphate, which has been reported to enhance high-intensity endurance exercise, may be a more affordable alternative to creatine phosphate. Secondly, a creatine/HMB combination was reported to be more effective at improving LBM and strength than either supplement alone [39], but other data has reported the combination offers no benefit in terms of increasing aerobic or anaerobic capacity [40,41]. The conflicting data therefore do not warrant recommendation of the creatine/HMB combination in lieu of CM. Lastly, creatine + glycerol has been reported to increase total body water as a hyper-hydration method prior to exercise in the heat, but this is also the first study of its kind. In addition, this combination failed to improve thermal and cardiovascular responses to a greater extent than CM alone [42].

The addition of nutrients that increase insulin levels and/or improve insulin sensitivity has been a major source of interest in the last few years by scientists looking to optimize the ergogenic effects of creatine. The addition of certain macronutrients appears to significantly augment muscle retention of creatine. Green et al. [24] reported that adding 93 g of carbohydrate to 5 g of CM increased total muscle creatine by 60%. Likewise, Steenge et al. [23] reported that adding 47 g of carbohydrate and 50 g of protein to CM was as effective at promoting muscle retention of creatine as adding 96 g of carbohydrate. Additional investigations by Greenwood and colleagues [30,43] have reported increased creatine retention from the addition of dextrose or low levels of D-pinitol (a plant extract with insulin-like properties). While the addition of these nutrients has proved to increase muscle retention, several recent investigations have reported these combinations to be no more effective at improving muscle strength and endurance or athletic performance [44-46]. Other recent studies, however, have indicated a

potential benefit on anaerobic power, muscle hypertrophy, and 1 RM muscle strength when combining protein with creatine [47,48]. It appears that combining CM with carbohydrate or carbohydrate and protein produces optimal results. Studies suggest that increasing skeletal muscle creatine uptake may enhance the benefits of training.

Effects of Supplementation on Exercise Performance and Training Adaptations

CM appears to be the most effective nutritional supplement currently available in terms of improving lean body mass and anaerobic capacity. To date, several hundred peer-reviewed research studies have been conducted to evaluate the efficacy of CM supplementation in improving exercise performance. Nearly 70% of these studies have reported a significant improvement in exercise capacity, while the others have generally reported non-significant gains in performance [49]. No studies have reported an ergolytic effect on performance although some have suggested that weight gain associated with CM supplementation could be detrimental in sports such as running or swimming. The average gain in performance from these studies typically ranges between 10 to 15% depending on the variable of interest. For example, short-term CM supplementation has been reported to improve maximal power/strength (5–15%), work performed during sets of maximal effort muscle contractions (5–15%), single-effort sprint performance (1–5%), and work performed during repetitive sprint performance (5–15%) [49]. Long-term CM supplementation appears to enhance the overall quality of training, leading to 5 to 15% greater gains in strength and performance [49]. Nearly all studies indicate that "proper" CM supplementation increases body mass by about 1 to 2 kg in the first week of loading [19].

The vast expanse of literature confirming the effectiveness of CM supplementation is far beyond the scope of this review. Briefly, short-term adaptations reported from CM supplementation include increased cycling power, total work performed on the bench press and jump squat, as well as improved sport performance in sprinting, swimming, and soccer [38,50-57]. Long-term adaptations when combining CM supplementation with training include increased muscle creatine and PCr content, lean body mass, strength, sprint performance, power, rate of force development, and muscle diameter [39,54-60]. In long-term studies, subjects taking CM typically gain about twice as much body mass and/or fat free mass (i.e., an extra 2 to 4 pounds of muscle mass during 4 to 12 weeks of training) than subjects taking a placebo [61-64]. The gains in muscle mass appear to be a result of an improved ability to perform high-intensity exercise via increased PCr availability and enhanced ATP synthesis, thereby enabling an athlete to train harder and promote greater muscular hypertrophy via increased myosin heavy chain expression possibly due to an increase in myogenic regulatory factors myogenin and MRF-4 [26,27,65]. The tremendous numbers of investigations conducted with positive results from CM supplementation lead us to conclude that it is the most effective nutritional supplement available today for increasing high-intensity exercise capacity and building lean mass.

Medical Safety of Creatine Supplementation

While the only clinically significant side effect reported in the research literature is that of weight gain [4,18,22], many anecdotal claims of side effects including dehydration, cramping, kidney and liver damage, musculoskeletal injury, gastrointestinal distress, and anterior (leg) compartment syndrome still exist in the media and popular literature. While athletes who are taking CM may experience these symptoms, the scientific literature suggests that these athletes have no greater, and a possibly lower, risk of these symptoms than those not supplementing with CM [2,4,66,67].

Many of these fears have been generated by the media and data taken from case studies (n = 1). Poortmans and Francaux reported that the claims of deleterious effects of creatine supplements on renal function began in 1998 [68]. These claims followed a report that creatine supplementation was detrimental to renal glomerular filtration rate (GFR) in a 25-year-old man who had previously presented

with kidney disease (glomerulosclerosis and corticosteroid-responsive nephritic syndrome) [69]. Three days later, a French sports newspaper, *L'Equipe*, reported that supplemental creatine is dangerous for the kidneys in any condition [70]. Several European newspapers then picked up the "news" and reported the same. Since that time, other individual case studies have been published posing that CM supplementation caused deleterious effects on renal function [71,72].

Much of the concern about CM supplementation and renal function has centered around concerns over increased serum creatinine levels. While creatinine does make up a portion of GFR and must be excreted by the kidneys, there is no evidence to support the notion that normal creatine intakes (< 25 g/d) in healthy adults cause renal dysfunction. In fact, Poortmans et al. have shown no detrimental effects of short- (5 days), medium- (14 days), or long-term (10 months to 5 years) CM supplementation on renal function [5,73,74]. Interestingly, Kreider et al. [4] observed no significant difference in creatinine levels between CM users and controls, yet most athletes (regardless of whether taking CM or not) had elevated creatinine levels along with proper clearance during intense training. The authors noted that if serum creatinine was examined as the sole measure of renal function, it would appear that nearly all of the athletes (regardless of CM usage) were experiencing renal distress. Although case studies have reported problems, these large-scale, controlled studies have shown no evidence indicating that CM supplementation in healthy individuals is a detriment to kidney functioning.

Another anecdotal complaint about supplemental creatine is that the long-term effects are not known. Widespread use of CM began in the 1990's. Over the last few years a number of researchers have begun to release results of long-term safety trials. So far, no long-term side effects have been observed in athletes (up to 5 years), infants with creatine synthesis deficiency (up to 3 years), or in clinical patient populations (up to 5 years) [4,5,18,75,76]. One cohort of patients taking 1.5 – 3 grams/day of CM has been monitored since 1981 with no significant side effects [77,78]. In addition, research has demonstrated a number of potentially helpful clinical uses of CM in heart patients, infants and patients with creatine synthesis deficiency, patients suffering orthopedic injury, and patients with various neuromuscular diseases. Potential medical uses of supplemental creatine have been investigated since the mid 1970s. Initially, research focused on the role of CM and/or creatine phosphate in reducing heart arrhythmias and/or improving heart function during ischemic events [18]. Interest in medical uses of creatine supplements has expanded to include those with creatine deficiencies [79-81], brain and/or spinal cord injuries [82-86], muscular dystrophy [87-90], diabetes [91], high cholesterol/triglyceride levels [92], and pulmonary disease [93] among others. Although more research is needed to determine the extent of the clinical utility, some promising results have been reported in a number of studies suggesting that creatine supplements may have therapeutic benefit in certain patient populations. In conjunction with short- and long-term studies in healthy populations, this evidence suggests that creatine supplementation appears to be safe when taken within recommended usage guidelines.

Creatine Use in Children and Adolescents

Opponents of creatine supplementation have claimed that it is not safe for children and adolescents [1]. While fewer investigations have been conducted in using younger participants, no study has shown CM to have adverse effects in children. In fact, long-term CM supplementation (e.g., 4 – 8 grams/day for up to 3 years) has been used as an adjunctive therapy for a number of creatine synthesis deficiencies and neuromuscular disorders in children. Clinical trials are also being conducted in children with Duschenne muscular dystrophy [87,88]. However, as less is known about the effects of supplemental creatine on children and adolescents, it is the view of the ISSN that younger athletes should consider a creatine supplement only if the following conditions are met [19]:

1. The athlete is past puberty and is involved in serious/competitive training that may benefit from

creatine supplementation;

2. The athlete is eating a well-balanced, performance-enhancing diet;

3. The athlete and his/her parents understand the truth concerning the effects of creatine supplementation;

4. The athlete's parents approve that their child takes supplemental creatine;

5. Creatine supplementation can be supervised by the athletes parents, trainers, coaches, and/or physician;

6. Quality supplements are used; and,

7. The athlete does not exceed recommended dosages.

If these conditions are met, then it would seem reasonable that high school athletes should be able to take a creatine supplement. Doing so may actually provide a safe nutritional alternative to illegal anabolic steroids or other potentially harmful drugs. Conversely, if the above conditions are not met, then creatine supplementation may not be appropriate. It appears that this is no different than teaching young athletes' proper training and dietary strategies to optimize performance. Creatine is not a panacea or short cut to athletic success. It can, however, offer some benefits to optimize training of athletes involved in intense exercise in a similar manner that ingesting a high-carbohydrate diet, sports drinks, and/or carbohydrate loading can optimize performance of an endurance athlete.

The Ethics of Creatine

Several athletic governing bodies and special interest groups have questioned whether it is ethical for athletes to take creatine supplements as a method of enhancing performance. Since research indicates that CM can improve performance, and it would be difficult to ingest enough creatine from food in the diet, they rationalize that it is unethical to do so. In this age of steroid suspicion in sports, some argue that if you allow athletes to take creatine, they may be more predisposed to try other dangerous supplements and/or drugs. Still others have attempted to directly lump creatine in with anabolic steroids and/or banned stimulants and have called for a ban on the use of CM and other supplements among athletes. Finally, fresh off of the ban of dietary supplements containing ephedra, some have called for a ban on the sale of CM citing safety concerns. Creatine supplementation is not currently banned by any athletic organization although the NCAA does not allow institutions to provide CM or other "muscle building" supplements to their athletes (e.g., protein, amino acids, HMB, etc). In this case, athletes must purchase creatine containing supplements on their own. The International Olympic Committee considered these arguments and ruled that there was no need to ban creatine supplements since creatine is readily found in meat and fish and there is no valid test to determine whether athletes are taking it. In light of the research that has been conducted with CM, it appears that those who call for a ban on it are merely familiar with the anecdotal myths surrounding the supplement, and not the actual facts. We see no difference between creatine supplementation and ethical methods of gaining athletic advantage such as using advanced training techniques and proper nutritional methods. Carbohydrate loading is a nutritional technique used to enhance performance by enhancing glycogen stores. We see no difference between such a practice and supplementing with creatine to enhance skeletal muscle creatine and PCr stores. If anything, it could be argued that banning the use of creatine would be unethical as it has been reported to decrease the incidence of musculoskeletal injuries [2,66,75,94], heat stress [2,95,96], provide neuroprotective effects [82,83,85,97,98], and expedite rehabilitation from injury [86,99,100].

Conclusion

It is the position of the International Society of Sports Nutrition that the use of creatine as a nutritional supplement within established guidelines is safe, effective, and ethical. Despite lingering myths concerning creatine supplementation in conjunction with exercise, CM remains one of the most extensively studied, as well as effective, nutritional aids available to athletes. Hundreds of studies have shown the effectiveness of CM supplementation in improving anaerobic capacity, strength, and lean body mass in conjunction with training. In addition, CM has repeatedly been reported to be safe, as well as possibly beneficial in preventing injury. Finally, the future of creatine research looks bright in regard to the areas of transport mechanisms, improved muscle retention, as well as treatment of numerous clinical maladies via supplementation.

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EXHIBIT 25

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Creatine supplementation with specific view to exercise/sports performance: an update

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Abstract

Creatine is one of the most popular and widely researched natural supplements. The majority of studies have focused on the effects of creatine monohydrate on performance and health; however, many other forms of creatine exist and are commercially available in the sports nutrition/supplement market. Regardless of the form, supplementation with creatine has regularly shown to increase strength, fat free mass, and muscle morphology with concurrent heavy resistance training more than resistance training alone. Creatine may be of benefit in other modes of exercise such as high-intensity sprints or endurance training. However, it appears that the effects of creatine diminish as the length of time spent exercising increases. Even though not all individuals respond similarly to creatine supplementation, it is generally accepted that its supplementation increases creatine storage and promotes a faster regeneration of adenosine triphosphate between high intensity exercises. These improved outcomes will increase performance and promote greater training adaptations. More recent research suggests that creatine supplementation in amounts of 0.1 g/kg of body weight combined with resistance training improves training adaptations at a cellular and sub-cellular level. Finally, although presently ingesting creatine as an oral supplement is considered safe and ethical, the perception of safety cannot be guaranteed, especially when administered for long period of time to different populations (athletes, sedentary, patient, active, young or elderly).

Introduction

Creatine is produced endogenously at an amount of about 1 g/d. Synthesis predominately occurs in the liver, kidneys, and to a lesser extent in the pancreas. The remainder of the creatine available to the body is obtained through the diet at about 1 g/d for an omnivorous diet. 95% of the bodies creatine stores are

found in the skeletal muscle and the remaining 5% is distributed in the brain, liver, kidney, and testes [1]. As creatine is predominately present in the diet from meats, vegetarians have lower resting creatine concentrations [2].

Creatine is used and researched in a clinical setting to investigate various pathologies or disorders such as myopathies [3,4] and is also used as an ergogenic aid for improving health and sports performance in athletes [5]. As an oral supplement, the most widely used and researched form is creatine monohydrate (CM). When orally ingested, CM has shown to improve exercise performance and increase fat free mass [5-9].

There is a great amount of research published on creatine supplementation; protocols of administration, forms of creatine, as well as potential side effects. Despite this, the mechanisms by which creatine acts in the human body to improve physical and cognitive performance are still not clear. The main objectives of this review are to analyze the more recent findings on the effects and mechanisms of creatine supplementation in sports and health. As a secondary purpose, we will analyze the most recommended protocols of ingestion and its potential side effects.

Creatine metabolism

The majority of creatine in the human body is in two forms, either the phosphorylated form making up 60% of the stores or in the free form which makes up 40% of the stores. The average 70 kg young male has a creatine pool of around 120-140 g which varies between individuals [10,11] depending on the skeletal muscle fiber type [1] and quantity of muscle mass [11]. The endogenous production and dietary intake matches the rate of creatinine production from the degradation of phosphocreatine and creatine at 2.6% and 1.1%/d respectively. In general, oral creatine supplementation leads to an increase of creatine levels within the body. Creatine can be cleared from the blood by saturation into various organs and cells or by renal filtration [1].

Three amino acids (glycine, arginine and methionine) and three enzymes (L-arginine:glycine amidinotransferase, guanidinoacetate methyltransferase and methionine adenosyltransferase) are required for creatine synthesis. The impact creatine synthesis has on glycine metabolism in adults is low, however the demand is more appreciable on the metabolism of arginine and methionine [11].

Creatine ingested through supplementation is transported into the cells exclusively by CreaT1. However, there is another creatine transporter Crea T2, which is primarily active and present in the testes [12]. Creatine uptake is regulated by various mechanisms, namely phosphorylation and glycosylation as well as extracellular and intracellular levels of creatine. Crea T1 has shown to be highly sensitive to the extracellular and intracellular levels being specifically activated when total creatine content inside the cell decreases [12]. It has also been observed that in addition to cytosolic creatine, the existence of a mitochondrial isoform of Crea T1 allows creatine to be transported into the mitochondria. Indicating another intra-mitochondrial pool of creatine, which seems to play an essential role in the phosphate-transport system from the mitochondria to the cytosol [13]. Myopathy patients have demonstrated reduced levels of total creatine and phosphocreatine as well as lower levels of CreaT1 protein, which is thought to be a major contributor to these decreased levels [14].

Documented effects of creatine supplementation on physical performance

The majority of studies focusing on creatine supplementation report an increase in the body's' creatine pool [15-17]. There is a positive relationship between muscle creatine uptake and exercise performance [17]. Volek et al [18] observed a significant increase in strength performance after 12 weeks creatine supplementation with a concurrent periodized heavy resistance training protocol. The creatine supplementation protocol consisted of a weeklong loading period of 25 g/d followed by a 5 g

maintenance dose for the remainder of the training. These positive effects were attributed to an increased total creatine pool resulting in more rapid adenosine triphosphate (ATP) regeneration between resistance training sets allowing athletes to maintain a higher training intensity and improve the quality of the workouts along the entire training period.

It is regularly reported that creatine supplementation, when combined with heavy resistance training leads to enhanced physical performance, fat free mass, and muscle morphology [18-22]. A 2003 meta analysis [8] showed individuals ingesting creatine, combined with resistance training, obtain on average +8% and +14% more performance on maximum (1RM) or endurance strength (maximal repetitions at a given percent of 1RM) respectively than the placebo groups. However, contradicting studies have reported no effects of creatine supplementation on strength performance. Jakobi et al [23] found no effects of a short term creatine loading protocol upon isometric elbow flexion force, muscle activation, and recovery process. However, this study did not clearly state if creatine supplementation was administered concurrent with resistance training. Bemben et al [24] have shown no additional benefits of creatine alone or combined with whey protein for improving strength and muscle mass after a progressive 14 weeks (3 days per week) resistance training program in older men. These conflicting results can be explained by the possibility that the supplemented groups were formed by a greater amount of non-responders or even because creatine supplementation was administered on the training days only (3 times a week). This strategy has not been adequately tested as effective in middle aged and older men for maintaining post loading elevated creatine stores [5].

A quantitative, comprehensive scientific summary and view of knowledge up to 2007 on the effects of creatine supplementation in athletes and active people was published in a 100 citation review position paper by the *International Society of Sports Nutrition*[5]. More recent literature has provided greater insight into the anabolic/performance enhancing mechanisms of creatine supplementation [15,25] suggesting that these effects may be due to satellite cell proliferation, myogenic transcription factors and insulin-like growth factor-1 signalling [16]. Saremi et al [26] reported a change in myogenic transcription factors when creatine supplementation and resistance training are combined in young healthy males. It was found that serum levels of myostatin, a muscle growth inhibitor, were decreased in the creatine group.

Collectively, in spite of a few controversial results, it seems that creatine supplementation combined with resistance training would amplify performance enhancement on maximum and endurance strength as well muscle hypertrophy.

Effects of creatine supplementation on predominantly anaerobic exercise

Creatine has demonstrated neuromuscular performance enhancing properties on short duration, predominantly anaerobic, intermittent exercises. Bazzucch et al [27] observed enhanced neuromuscular function of the elbow flexors in both electrically induced and voluntary contractions but not on endurance performance after 4 loading doses of 5 g creatine plus 15 g maltodextrin for 5/d in young, moderately trained men. Creatine supplementation may facilitate the reuptake of Ca^{2+} into the sacroplasmic reticulum by the action of the Ca^{2+} adenosine triphosphatase pump, which could enable force to be produced more rapidly through the faster detachment of the actomyosin bridges.

A previous meta-analysis [28] reported an overall creatine supplementation effect size (ES) of 0.24 ± 0.02 for activities lasting ≤30 s. (primarily using the ATP- phosphocreatine energy system). For this short high-intensity exercise, creatine supplementation resulted in a $7.5 \pm 0.7\%$ increase from base line which was greater than the $4.3 \pm 0.6\%$ improvement observed for placebo groups. When looking at the individual selected measures for anaerobic performance the greatest effect of creatine supplementation was observed on the number of repetitions which showed an ES of 0.64 ± 0.18. Furthermore, an

increase from base line of 45.4 ± 7.2% compared to 22.9 ± 7.3% for the placebo group was observed. The second greatest ES was on the weight lifted at 0.51 ± 0.16 with an increase from base line of 13.4 ± 2.7% for the placebo group and 24.7 ± 3.9% for the creatine group. Other measures improved by creatine with a mean ES greater than 0 were for the amount of work accomplished, weight lifted, time, force production, cycle ergometer revolutions/min and power. The possible effect of creatine supplementation on multiple high intensity short duration bouts (<30 s) have shown an ES not statistically significant from 0. This would indicate that creatine supplementation might be useful to attenuate fatigue symptoms over multiple bouts of high-intensity, short duration exercise. The ES of creatine on anaerobic endurance exercise (>30 – 150s), primarily using the anaerobic glycolysis energy system, was 0.19 ± 0.05 with an improvement from baseline of 4.9 ± 1.5 % for creatine and -2.0 ± 0.6% for the placebo. The specific aspects of anaerobic endurance performance improved by creatine supplementation were work and power, both of which had a mean ES greater than 0. From the findings of this previous meta-analysis [28] it would appear that creatine supplementation has the most pronounced effect on short duration (<30s) high intensity intermittent exercises.

Effects of creatine supplementation on skeletal muscle hypertrophy

Cribb et al (2007) [29] observed greater improvements on 1RM, lean body mass, fiber cross sectional area and contractile protein in trained young males when resistance training was combined with a multi-nutrient supplement containing 0.1 g/kg/d of creatine, 1.5 g/kg/d of protein and carbohydrate compared with protein alone or a protein carbohydrate supplement without the creatine. These findings were novel because at the time no other research had noted such improvements in body composition at the cellular and sub cellular level in resistance trained participants supplementing with creatine. The amount of creatine consumed in the study by Cribb et al was greater than the amount typically reported in previous studies (a loading dose of around 20 g/d followed by a maintenance dose of 3-5 g/d is generally equivalent to approximately 0.3 g/kg/d and 0.03 g/kg/d respectively) and the length of the supplementation period or absence of resistance exercise may explain the observed transcriptional level changes that were absent in previous studies [30,31].

Deldicque et al [32] found a 250%, 45% and 70% increase for collagen mRNA, glucose transporter 4 (GLUT4) and Myosin heavy chain IIA, respectively after 5 days creatine loading protocol (21 g/d). The authors speculated that creatine in addition to a single bout of resistance training can favor an anabolic environment by inducing changes in gene expression after only 5 days of supplementation.

When creatine supplementation is combined with heavy resistance training, muscle insulin like growth factor (IGF-1) concentration has been shown to increase. Burke et al [2] examined the effects of an 8 week heavy resistance training protocol combined with a 7 day creatine loading protocol (0.25 g/d/kg lean body mass) followed by a 49 day maintenance phase (0.06 g/kg lean mass) in a group of vegetarian and non-vegetarian, novice, resistance trained men and women. Compared to placebo, creatine groups produced greater increments in IGF-1 (78% Vs 55%) and body mass (2.2 Vs 0.6 kg). Additionally, vegetarians within the supplemented group had the largest increase of lean mass compared to non vegetarian (2.4 and 1.9 kg respectively). Changes in lean mass were positively correlated to the modifications in intramuscular total creatine stores which were also correlated with the modified levels of intramuscular IGF-1. The authors suggested that the rise in muscle IGF-1 content in the creatine group could be due to the higher metabolic demand created by a more intensely performed training session. These amplifying effects could be caused by the increased total creatine store in working muscles. Even though vegetarians had a greater increase in high energy phosphate content, the IGF-1 levels were similar to the amount observed in the non vegetarian groups. These findings do not support the observed correlation pattern by which a low essential amino acid content of a typical vegetarian diet should reduce IGF-1 production [33]. According to authors opinions it is possible that the addition of

creatine and subsequent increase in total creatine and phosphocreatine storage might have directly or indirectly stimulated production of muscle IGF-I and muscle protein synthesis, leading to an increased muscle hypertrophy [2].

Effects of creatine supplementation on predominantly aerobic exercise

Although creatine supplementation has been shown to be more effective on predominantly anaerobic intermittent exercise, there is some evidence of its positive effects on endurance activities. Branch [28] highlights that endurance activities lasting more than 150s rely on oxidative phosphorylation as primary energy system supplier. From this meta analysis [28], it would appear that the ergogenic potential for creatine supplementation on predominantly aerobic endurance exercise diminishes as the duration of the activity increases over 150s. However it is suggested that creatine supplementation may cause a change in substrate utilization during aerobic activity possibly leading to an increase in steady state endurance performance.

Chwalbinska-Monteta [34] observed a significant decrease in blood lactate accumulation when exercising at lower intensities as well as an increase in lactate threshold in elite male endurance rowers after consuming a short loading (5 days 20 g/d) CM protocol. However, the effects of creatine supplementation on endurance performance have been questioned by some studies. Graef et al [35] examined the effects of four weeks of creatine citrate supplementation and high-intensity interval training on cardio respiratory fitness. A greater increase of the ventilatory threshold was observed in the creatine group respect to placebo; however, oxygen consumption showed no significant differences between the groups. The total work presented no interaction and no main effect for time for any of the groups. Thompson et al [36] reported no effects of a 6 week 2 g CM/d in aerobic and anaerobic endurance performance in female swimmers. In addition, of the concern related to the dosage used in these studies, it could be possible that the potential benefits of creatine supplementation on endurance performance were more related to effects of anaerobic threshold localization.

Effects of creatine supplementation on glycogen stores

It is suggested [16,37] that another mechanism for the effect of creatine could be enhanced muscle glycogen accumulation and GLUT4 expression, when creatine supplementation is combined with a glycogen depleting exercise. Whereas it has been observed [38] that creatine supplementation alone does not enhance muscle glycogen storage. Hickner et al [15] observed positive effects of creatine supplementation for enhancing initial and maintaining a higher level of muscle glycogen during 2 hours of cycling. In general, it is accepted that glycogen depleting exercises, such as high intensity or long duration exercise should combine high carbohydrate diets with creatine supplementation to achieve heightened muscle glycogen stores [39].

Effects of creatine ingestion to improve recovery from injury, muscle damage and oxidative stress induced by exercise

Creatine supplementation may also be of benefit to injured athletes. Op't Eijnde et al [39] noted that the expected decline in GLUT4 content after being observed during a immobilization period can be offset by a common loading creatine (20g/d) supplementation protocol. In addition, combining CM 15g/d for 3 weeks following 5 g/d for the following 7 weeks positively enhances GLUT4 content, glycogen, and total muscle creatine storage [39].

Bassit et al [40] observed a decrease in several markers of muscle damage (creatine kinase, lactate dehydrogenase, aldolase, glutamic oxaloacetic acid transaminase and glutamic pyruvic acid transaminase) in 4 athletes after an iron man competition who supplemented with 20 g/d plus 50 g

maltodextrin during a 5 d period prior to the competition.

Cooke et al [41] observed positive effects of a prior (0.3 g/d kg BW) loading and a post maintenance protocol (0.1 g/d kg BW) to attenuate the loss of strength and muscle damage after an acute supramaximal (3 set x 10 rep with 120% 1RM) eccentric resistance training session in young males. The authors speculate that creatine ingestion prior to exercise may enhance calcium buffering capacity of the muscle and reduce calcium-activated proteases which in turn minimize sarcolemma and further influxes of calcium into the muscle. In addition creatine ingestion post exercise would enhance regenerative responses, favoring a more anabolic environment to avoid severe muscle damage and improve the recovery process. In addition, in vitro studies have demonstrated the antioxidant effects of creatine to remove superoxide anion radicals and peroxinitrite radicals [42]. This antioxidant effect of creatine has been associated with the presence of Arginine in its molecule. Arginine is also a substrate for nitric oxide synthesis and can increase the production of nitric oxide which has higher vasodilatation properties, and acts as a free radical that modulates metabolism, contractibility and glucose uptake in skeletal muscle. Other amino acids contained in the creatine molecule such as glycine and methinine may be especially susceptible to free radical oxidation because of sulfhydryl groups [42]. A more recent in vitro study showed that creatine exerts direct antioxidant activity via a scavenging mechanism in oxidatively injured cultured mammalian cells [43]. In a recent in vivo study Rhaini et al [44] showed a positive effect of 7 days of creatine supplementation (4 x 5 g CM 20 g total) on 27 recreational resistance trained males to attenuate the oxidation of DNA and lipid peroxidation after a strenuous resistance training protocol.

Collectively the above investigations indicate that creatine supplementation can be an effective strategy to maintain total creatine pool during a rehabilitation period after injury as well as to attenuate muscle damage induced by a prolonged endurance training session. In addition, it seems that creatine can act as an effective antioxidant agent after more intense resistance training sessions.

Effects of creatine supplementation on range of motion

Sculthorpe et al (2010) has shown that a 5 day (25g/d) loading protocol of creatine supplementation followed by a further 3 days of 5 g/d negatively influence both active ankle dorsiflexion and shoulder abduction and extension range of movement (ROM) in young men. There are two possible theories to explain these effects: 1) Creatine supplementation increases intracellular water content resulting in increased muscle stiffness and resistance to stretch; 2) Neural outflow from the muscle spindles is affected due to an increased volume of the muscle cell. The authors highlight that the active ROM measures were taken immediately after the loading phase and the reduced active ROM may not be seen after several weeks of maintenance phase [45]. Hile et al [46] observed an increase in compartment pressure in the anterior compartment of the lower leg, which may also have been responsible for a reduced active ROM.

Documented effects of creatine supplementation for health and clinical setting

Neurological and cognitive function has also been shown to be improved by creatine supplementation [47,48]. Rawson and Venezia [49] review the effects of creatine supplementation on cognitive function highlighting that higher brain creatine has been associated with improved neuropsychological performance. Creatine supplementation protocols have been shown to increase brain creatine and phosphocreatine contents. Cognitive processing hindered due to sleep deprivation and natural impairment due to aging can be improved by creatine supplementation. This review also highlights other possible benefits of creatine ingestion to older adults, such as improvements in: fatigue resistance, strength, muscle mass, bone mineral density, and performance of activities of daily living. Some of these benefits occur without concurrent exercise. The authors inform that discrepancies between studies

do exist and are hard to explain but may be possibly due to differences in diet, race and/or supplementation protocols. However, the ideal dose of creatine to maximize brain uptake is not known. Patients have been supplemented with 40 g while in healthy adults positive results have been reported with around 20 g per day [49].

Studies with animal and cellular models demonstrated positive effect of creatine ingestion on neurodegenerative diseases. These effects have been attributed to improved overall cellular bioenergetics due to an expansion of the phosphocreatine pool [50]. Creatine deficiency syndromes, due to deficiency of glycine amidinotransferase and guanidinoacetate methyltransferase, can cause decreases or complete absence of creatine in the central nervous system. Syndromes of this nature have the possibility to be improved by supplementing orally with creatine. Brain creatine deficiency resulting from ineffective crea T1 has been shown not to be effectively treated with oral creatine supplementation [51]. Additionally, oral creatine administration in patients with myopathies has shown conflicting results depending on the type of myopathy and creatine transport systems disorders [4].

Creatine use in children and adolescents

Creatine supplementation in the under 18 population has not received a great deal of attention, especially in regards to sports/exercise performance. Despite this, creatine is being supplemented in young, <18 years old, athletes [52,53]. In a 2001 report [52] conducted on pupils from middle and high school (aged 10 – 18) in Westchester County (USA) 62 of the 1103 pupils surveyed were using creatine. The authors found this concerning for 2 main reasons: firstly, the safety of creatine supplementation is not established for this age group and is therefore not recommended. Secondly, it was speculated that taking creatine would lead on to more dangerous performance enhancing products such as anabolic steroids. It is important to point out that this potential escalation is speculation. Furthermore, a questionnaire was used to determine creatine use amongst this age group and does not necessarily reflect the truth.

A child's ability to regenerate high energy phosphates during high intensity exercise is less than that of an adult. Due to this, creatine supplementation may benefit the rate and use of creatine phosphate and ATP rephosporylation. However, performance in short duration high-intensity exercise can be improved through training therefore supplementation may not be necessary [54].

Based on the limited data on performance and safety, some authors have not identified any conclusions and do not recommend its consumption in regards to creatine supplementation in children and adolescents [52,54]. Conversely, according to the view of the ISSN [5], younger athletes should consider a creatine supplement under certain conditions: puberty is past and he/she is involved in serious competitive training; the athlete is eating a well-balanced caloric adequate diet; he/she as well as the parents approve and understand the truth concerning the effects of creatine supplementation; supplement protocols are supervised by qualified professionals; recommended doses must not be exceeded; quality supplements are administered.

Within this framework, creatine supplementation in young, post puberty athletes can be considered a high quality type of "food" that can offer additional benefits to optimise training outcomes.

Dosing protocols applied in creatine supplementation

A typical creatine supplementation protocol consists of a loading phase of 20 g CM/d or 0.3 g CM/kg/d split into 4 daily intakes of 5 g each, followed by a maintenance phase of 3-5 g CM/d or 0.03 g CM/kg/d for the duration of the supplementation period [5]. Other supplementation protocols are also used such as a daily single dose of around 3 – 6 g or between 0.03 to 0.1 g/kg/d [15,55] however this method takes longer (between 21 to 28 days) to produce ergogenic effects [5]. Sale et al [56] found that

a moderate protocol consisting of 20 g CM taken in 1g doses (evenly ingested at 30-min intervals) for 5 days resulted in reduced urinary creatine and methylamine excretion, leading to an estimated increase in whole body retention of creatine (+13%) when compared with a typical loading supplementation protocol of 4 x 5 g/d during 5 days (evenly ingested at 3 hour intervals). This enhancement in creatine retention would lead to a significantly higher weight gain when people follow a moderate protocol ingestion of several doses of small amounts of CM evenly spread along the day.

Responders vs. non-responders

Syrotuik and Bell [57] investigated the physical characteristics of responder and non-responder subjects to creatine supplementation in recreationally resistance trained men with no history of CM usage. The supplement group was asked to ingest a loading dosage of 0.3 g/kg/d for 5 days. The physiological characteristics of responders were classified using Greenhaff et al [58] criterion of >20 mmol/kg dry weight increase in total intramuscular creatine and phosphocreatine and non responders as <10 mmol/kg dry weight increase, a third group labeled quasi responders were also used to classify participants who fell in between the previously mentioned groups (10-20 mmol/kg dry weight). Overall, the supplemented group showed a mean increase in total resting muscle creatine and phosphocreatine of 14.5% (from 111.12 ± 8.87 mmol/kg dry weight to 127.30 ± 9.69 mmol/kg dry weight) whilst the placebo group remained relatively unaffected (from 115.70 ± 14.99 mmol/kg dry weight to 111.74 ± 12.95 mmol/kg dry weight). However when looking at individual cases from the creatine group the results showed a variance in response. From the 11 males in the supplemented group, 3 participants were responders (mean increase of 29.5 mmol/kg dry weight or 27%), 5 quasi responders (mean increase of 14.9 mmol/kg dry weight or 13.6%) and 3 non-responders (mean increase of 5.1 mmol/kg dry weight or 4.8%). Using muscle biopsies of the vastus lateralis, a descending trend for groups and mean percentage fiber type was observed. Responders showed the greatest percentage of type II fibers followed by quasi responders and non-responders. The responder and quasi responder groups had an initial larger cross sectional area for type I, type IIa and type IIx fibers. The responder group also had the greatest mean increase in the cross sectional area of all the muscle fiber types measured (type I, type IIa and type IIx increased 320, 971 and 840 μm^2 respectively) and non-responders the least (type I, type IIa and type IIx increased 60, 46 and 78 μm^2 respectively). There was evidence of a descending trend for responders to have the highest percentage of type II fibers; furthermore, responders and quasi responders possessed the largest initial cross sectional area of type I, IIa and IIx fibers. Responders were seen to have the lowest initial levels of creatine and phosphocreatine. This has also been observed in a previous study [17] which found that subjects whose creatine levels were around 150 mmol/Kg dry mass did not have any increments in their creatine saturation due to creatine supplementation, neither did they experience any increases of creatine uptake, phosphocreatine resynthesis and performance. This would indicate a limit maximum size of the creatine pool.

In summary responders are those individuals with a lower initial level of total muscle creatine content, greater population of type II fibers and possess higher potential to improve performance in response to creatine supplementation.

Commercially available forms of creatine

There are several different available forms of creatine: creatine anhydrous which is creatine with the water molecule removed in order to increase the concentration of creatine to a greater amount than that found in CM. Creatine has been manufactured in salt form: creatine pyruvate, creatine citrate, creatine malate, creatine phosphate, magnesium creatine, creatine oroate, Kre Alkalyn (creatine with baking soda). Creatine can also be manufactured in an ester form. Creatine ethyl ester (hydrochloride) is an example of this, as is creatine gluconate which is creatine bound to glucose. Another form is creatine

effervescent which is creatine citrate or CM with citric acid and bicarbonate. The citric acid and bicarbonate react to produce an effervescent effect. When mixed with water the creatine separates from its carrier leaving a neutrally charged creatine, allowing it to dissolve to a higher degree in water. Manufacturers claim that creatine effervescent has a longer and more stable life in solution. When di-creatine citrate effervescent was studied [59] for stability in solution it was found that the di-creatine citrate dissociates to citric acid and creatine in aqueous solutions which in turn forms CM and eventually crystallises out of the solution due to its low solubility. Some of the creatine may also convert to creatinine.

Jager et al [60] observed 1.17 and 1.29 greater peak plasma creatine concentration 1 hour after ingesting creatine pyruvate compared to isomolar amount of CM and creatine citrate respectively. However time to peak concentration, and velocity constants of absorption and elimination, was the same for all three forms of creatine. Although not measured in this study it is questionable that these small differences in plasma creatine concentrations would have any effect on the increase of muscle creatine uptake. Jäger et al [61] investigated the effects of 28-days of creatine pyruvate and citrate supplementation on endurance capacity and power measured during an intermittent handgrip (15 s effort per 45s rest) exercise in healthy young athletes. The authors used a daily dose protocol with the intention to slowly saturate muscle creatine stores. Both forms of creatine showed slightly different effects on plasma creatine absorption and kinetics. The two creatine salts significantly increased mean power but only pyruvate forms showed significant effects for increasing force and attenuating fatigability during all intervals. These effects can be attributed to an enhanced contraction and relaxation velocity as well as a higher blood flow and muscle oxygen uptake. On the other hand, the power performance measured with the citrate forms decreases with time and improvements were not significant during the later intervals. In spite of these positive trends further research is required about the effects of these forms of creatine as there is little or no evidence for their safety and efficacy. Furthermore the regularity status of the novel forms of creatine vary from country to country and are often found to be unclear when compared to that of CM [62].

In summary, creatine salts have been show to be less stable than CM. However the addition of carbohydrates could increase their stability [62]. The potential advantages of creatine salts over CM include enhanced aqueous solubility and bioavailability which would reduce their possible gastrointestinal adverse effects [63]. The possibility for new additional formulation such as tablets or capsules is interesting for its therapeutic application due to its attributed better dissolution kinetics and oral absorption compared to CM [63]. However more complete in vivo pharmaceutical analysis of creatine salts are required to fully elucidate their potential advantages/disadvantages over the currently available supplement formulations.

Creatine is a hydrophilic polar molecule that consists of a negatively charged carboxyl group and a positively charged functional group [64]. The hydrophilic nature of creatine limits its bioavailability [65]. In an attempt to increase creatines bioavailability creatine has been esterified to reduce the hydrophilicity; this product is known as creatine ethyl ester. Manufacturers of creatine ethyl ester promote their product as being able to by-pass the creatine transporter due to improved sarcolemmal permeability toward creatine [65]. Spillane et al [65] analyzed the effects of a 5 days loading protocol (0.30 g/kg lean mass) followed by a 42 days maintenance phase (0.075 g/kg lean mass) of CM or ethyl ester both combined with a resistance training program in 30 novice males with no previous resistance training experience. The results of this study [65] showed that ethyl ester was not as effective as CM to enhance serum and muscle creatine stores. Furthermore creatine ethyl ester offered no additional benefit for improving body composition, muscle mass, strength, and power. This research did not support the claims of the creatine ethyl ester manufacturers.

Polyethylene glycol is a non-toxic, water-soluble polymer that is capable of enhancing the absorption of creatine and various other substances [66]. Polyethylene glycol can be bound with CM to form polyethylene glycosylated creatine. One study [67] found that 5 g/d for 28 days of polyethylene glycosylated creatine was capable of increasing 1RM bench press in 22 untrained young men but not for lower body strength or muscular power. Body weight also did not significantly change in the creatine group which may be of particular interest to athletes in weight categories that require upper body strength. Herda et al [68] analyzed the effects of 5 g of CM and two smaller doses of polyethylene glycosylated creatine (containing 1.25 g and 2.5 g of creatine) administered over 30 days on muscular strength, endurance, and power output in fifty-eight healthy men. CM produced a significantly greater improvement in mean power and body weight meanwhile both CM and polyethylene glycosylated form showed a significantly ($p < 0.05$) greater improvement for strength when compared with control group. These strength increases were similar even though the dose of creatine in the polyethylene glycosylated creatine groups was up to 75% less than that of CM. These results seem to indicate that the addition of polyethylene glycol could increase the absorption efficiency of creatine but further research is needed before a definitive recommendation can be reached.

Creatine in combination with other supplements

Although creatine can be bought commercially as a standalone product it is often found in combination with other nutrients. A prime example is the combination of creatine with carbohydrate or protein and carbohydrate for augmenting creatine muscle retention [5] mediated through an insulin response from the pancreas [69]. Steenge et al [70] found that body creatine retention of 5 g CM was increased by 25% with the addition of 50 g of protein and 47 g of carbohydrate or 96 g carbohydrate when compared to a placebo treatment of 5 g carbohydrate. The addition of 10g of creatine to 75 g of dextrose, 2 g of taurine, vitamins and minerals, induced a change in cellular osmolarity which in addition to the expected increase in body mass, seems to produce an up regulation of large scale gene expression (mRNA content of genes and protein content of kinases involved in osmosensing and signal transduction, cytoskeleton remodelling, protein and glycogen synthesis regulation, satellite cell proliferation and differentiation, DNA replication and repair, RNA transcription control, and cell survival) [25]. Similar findings have also been reported for creatine monohydrate supplementation alone when combined with resistance training [71].

A commercially available pre-workout formula comprised of 2.05 g of caffeine, taurine and glucuronolactone, 7.9 g of L-leucine, L-valine, L-arginine and L-glutamine, 5 g of di-creatine citrate and 2.5 g of β-alanine mixed with 500 ml of water taken 10 minutes prior to exercise has been shown to enhance time to exhaustion during moderate intensity endurance exercise and to increase feelings of focus, energy and reduce subjective feelings of fatigue before and during endurance exercise due to a synergistic effect of the before mentioned ingredients [72]. The role of creatine in this formulation is to provide a neuroprotective function by enhancing the energy metabolism in the brain tissue, promoting antioxidant activities, improving cerebral vasculation and protecting the brain from hyperosmotic shock by acting as a brain cell osmolyte. Creatine can provide other neuroprotective benefits through stabilisation of mitochondrial membranes, stimulation of glutamate uptake into synaptic vesicles and balance of intracellular calcium homeostasis [72].

Safety and side effects of creatine supplementation

There have been a few reported renal health disorders associated with creatine supplementation [73,74]. These are isolated reports in which recommended dosages are not followed or there is a history of previous health complaints, such as renal disease or those taking nephrotoxic medication aggravated by creatine supplementation [73]. Specific studies into creatine supplementation, renal function and/or

safety conclude that although creatine does slightly raise creatinine levels there is no progressive effect to cause negative consequences to renal function and health in already healthy individuals when proper dosage recommendations are followed [73-77]. Urinary methylamine and formaldehyde have been shown to increase due to creatine supplementation of 20 g/d; this however did not bring the production outside of normal healthy range and did not impact on kidney function [56,78]. It has been advised that further research be carried out into the effects of creatine supplementation and health in the elderly and adolescent [73,75]. More recently, a randomized, double blind, 6 month resistance exercise and supplementation intervention [79] was performed on elderly men and women (age >65 years) in which subjects were assigned to either a supplement or placebo group. The supplement group was given 5 g CM, 2 g dextrose and 6 g conjugated linoleic acid/d, whilst the placebo group consumed 7 g dextrose and 6 g safflower oil/d. CM administration showed significantly greater effects to improve muscular endurance, isokinetic knee extension strength, fat free mass and to reduce fat mass compared to placebo. Furthermore the supplement group had an increase in serum creatinine but not creatinine clearance suggesting no negative effect on renal function.

Cornelissen et al [80] analyzed the effects of 1 week loading protocol (3 X 5 g/d CM) followed by a 3 month maintenance period (5 g/d) on cardiac patients involved in an endurance and resistance training program. Although CM supplementation did not significantly enhance performance, markers of renal and liver function were within normal ranges indicating the safety of the applied creatine supplementation protocol.

A retrospective study [81], that examined the effects of long lasting (0.8 to 4 years) CM supplementation on health markers and prescribed training benefits, suggested that there is no negative health effects (including muscle cramp or injuries) caused by long term CM consumption. In addition, despite many anecdotal claims, it appears that creatine supplementation would have positive influences on muscle cramps and dehydration [82]. Creatine was found to increase total body water possibly by decreasing the risk of dehydration, reducing sweat rate, lowering core body temperature and exercising heart rate. Furthermore, creatine supplementation does not increase symptoms nor negatively affect hydration or thermoregulation status of athletes exercising in the heat [83,84]. Additionally, CM ingestion has been shown to reduce the rate of perceived exertion when training in the heat [85].

It is prudent to note that creatine supplementation has been shown to reduce the body's endogenous production of creatine, however levels return to normal after a brief period of time when supplementation ceases [1,6]. Despite this creatine supplementation has not been studied/supplemented with for a relatively long period. Due to this, long term effects are unknown, therefore safety cannot be guaranteed. Whilst the long term effects of creatine supplementation remain unclear, no definitive certainty of either a negative or a positive effect upon the body has been determined for many health professionals and national agencies [19,78]. For example the French Sanitary Agency has banned the buying of creatine due to the unproven allegation that a potential effect of creatine supplementation could be that of mutagenicity and carcinogenicity from the production of heterocyclic amines [78]. Long term and epidemiological data should continue to be produced and collected to determine the safety of creatine in all healthy individuals under all conditions [78].

Conclusion and practical recommendations

The above review indicates that creatine supplementation has positive effects on:

· Amplifying the effects of resistance training for enhancing strength and hypertrophy [5,22,28].

· Improving the quality and benefits of high intensity intermittent speed training [21].

· Improving aerobic endurance performance in trials lasting more than 150s [7].

· Seems to produce positive effects on strength, power, fat free mass, daily living performance and neurological function in young and older people [49].

· Research on the mechanisms of creatines effect has progressed since 2007 showing an up regulation of gene expression when creatine is administered together with resistance training exercises.

· Regarding predominantly aerobic endurance performance, the increased bodies' creatine stores, seems to amplify favorable physiological adaptations such as: increased plasma volume, glycogen storage, improvements of ventilatory threshold and a possible reduction of oxygen consumption in sub maximal exercise.

A typical creatine supplementation protocol of either a loading phase of 20 to 25 g CM/d or 0.3 g CM/kg/d split into 4 to 5 daily intakes of 5 g each have been recommended to quickly saturate creatine stores in the skeletal muscle. However a more moderate protocol where several smaller doses of creatine are ingested along the day (20 intakes of 1 g every 30 min) could be a better approach to get a maximal saturation of the intramuscular creatine store. In order to keep the maximal saturation of body creatine, the loading phase must be followed by a maintenance period of 3-5 g CM/d or 0.03 g CM/kg/d. These strategies appear to be the most efficient way of saturating the muscles and benefitting from CM supplementation. However more recent research has shown CM supplementation at doses of 0.1 g/kg body weight combined with resistance training improves training adaptations at a cellular and sub-cellular level. Creatine retention by the body from supplementation appears to be promoted by about 25% from the simultaneous ingestion of carbohydrate and/or protein mediated through an increase in insulin secretion. This combination would produce a faster saturation rate but has not been shown to have a greater effect on performance.

Different forms of creatine in combination with other sports supplements as well as varying doses and supplementation methodology should continue to be researched in an attempt to understand further application of creatine to increase sports and exercise performance of varying disciplines. It is important to remain impartial when evaluating the safety of creatine ingested as a natural supplement. The available evidence indicates that creatine consumption is safe. This perception of safety cannot be guaranteed especially that of the long term safety of creatine supplementation and the various forms of creatine which are administered to different populations (athletes, sedentary, patient, active, young or elderly) throughout the globe.

Abbreviations

ATP, Adenosine triphosphate; CM, Creatine monohydrate; ES, Effect size; g/d, Grams per day; g/kg/d, Grams per kilogram of body mass per day; ROM, Range of movement.

Competing interests

Maxinutrition and the University of Greenwich are providing joint funding with to one of the author's PhD project; however, this does not affect the purpose of the review and its content.

Authors' contributions

All authors have read, reviewed and contributed to the final manuscript.

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